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MYELOSCOPY: INTRASPINAL ENDOSCOPY

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FOUR years ago, the principle of intraspinal endoscopy was adapted to the diagnosis of lesions affecting the cauda equina and lowermost spinal cord. Since that time, nearly 400 "myeloscopic" examinations have been carried out.

The instrument devised for the purpose, a myeloscope,*[1, 2] may be introduced between any of the lumbar spinous processes in much the same manner as an ordinary lumbar puncture needle. No known trauma to nerve roots has ensued.

The abnormal conditions recognizable by myeloscopy include varicose vessels; arachnoid adhesions of post-traumatic or postinflammatory origin; neoplasms; the presence of inflamed nerve roots associated with clinical neuritis; and the effects of a herniated nucleus pulposis or hypertrophied ligamentum flavum.

Myeloscopy has never before been performed on the living subject, although a similar procedure has been tried on the cadaver.[3, 4]

DESCRIPTION OF MYELOSCOPE

The myeloscope consists of several parts, of which one is an oval metal cannula (Fig. 2, *A*). This cannula houses a close-fitting obturator (Fig. 2, *C*) which facilitates insertion of the instrument. The obturator is equipped with a special guide needle (Fig. 2, *B*). Following introduction of the cannula, the illuminating and lens systems (Fig. 2, *D* and *E*) replace the obturator, rendering the apparatus ready for visualization (Fig. 1).

A. *Cannula.*—The cannula is an oval tubular sheath of thin metal, approximately 12 cm. in length, rated as No. 7 French (Fig. 2, *A*). Its distal or intraspinal portion is partially cut away on one side to allow lateral displacement of the illuminating system by the after-coming lens

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*Designed by the author and made by the American Cystoscope Makers, Inc., New York, N. Y.

system. This arrangement affords material reduction in the diameter of the cannula. The external end of the cannula is equipped with an adaptor to receive the obturator or the lighting system. The adaptor is provided with a right-angle stopcock in which any standard syringe may be fitted for purposes of irrigation, introduction of oxygen, or collection of cerebrospinal fluid. Along the side of the cannula is a millimeter scale to facilitate accurate insertion of the instrument.

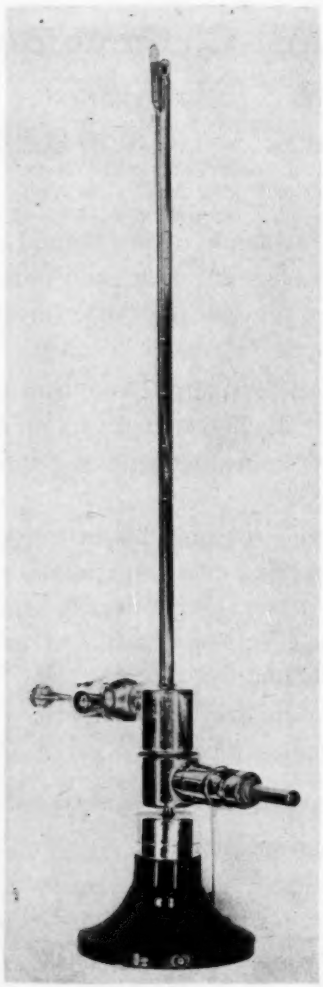

Fig. 1.—Myeloscope assembled for visualization.

B. *Obturator and Guide Needle.*—The obturator consists of a rigid metal tube which closely fits the lumen of the cannula (Fig. 2, *C*). Its tip, tapered to a point, extends approximately 1.6 mm. beyond the end of the cannula. Through the core of the obturator runs a No. 19 hollow "guide" needle (Fig. 2, *B*), which may be advanced well ahead of the obturator tip. The needle is provided with a stylet. On the handle of the needle there is a millimeter scale, corresponding to that on the

cannula. The needle is provided with a standard adaptor to which a spinal fluid manometer or syringe may be fitted.

C. *Illumination.*—The illuminating system consists of a small tubular carrier (Fig. 2, *D*) through which a wire runs to the miniature light socket at its tip. The socket is eccentrically placed so that when displaced through the lateral hiatus of the cannula tip, the light bulb lies outside the cannula. The proximal end of the light carrier terminates

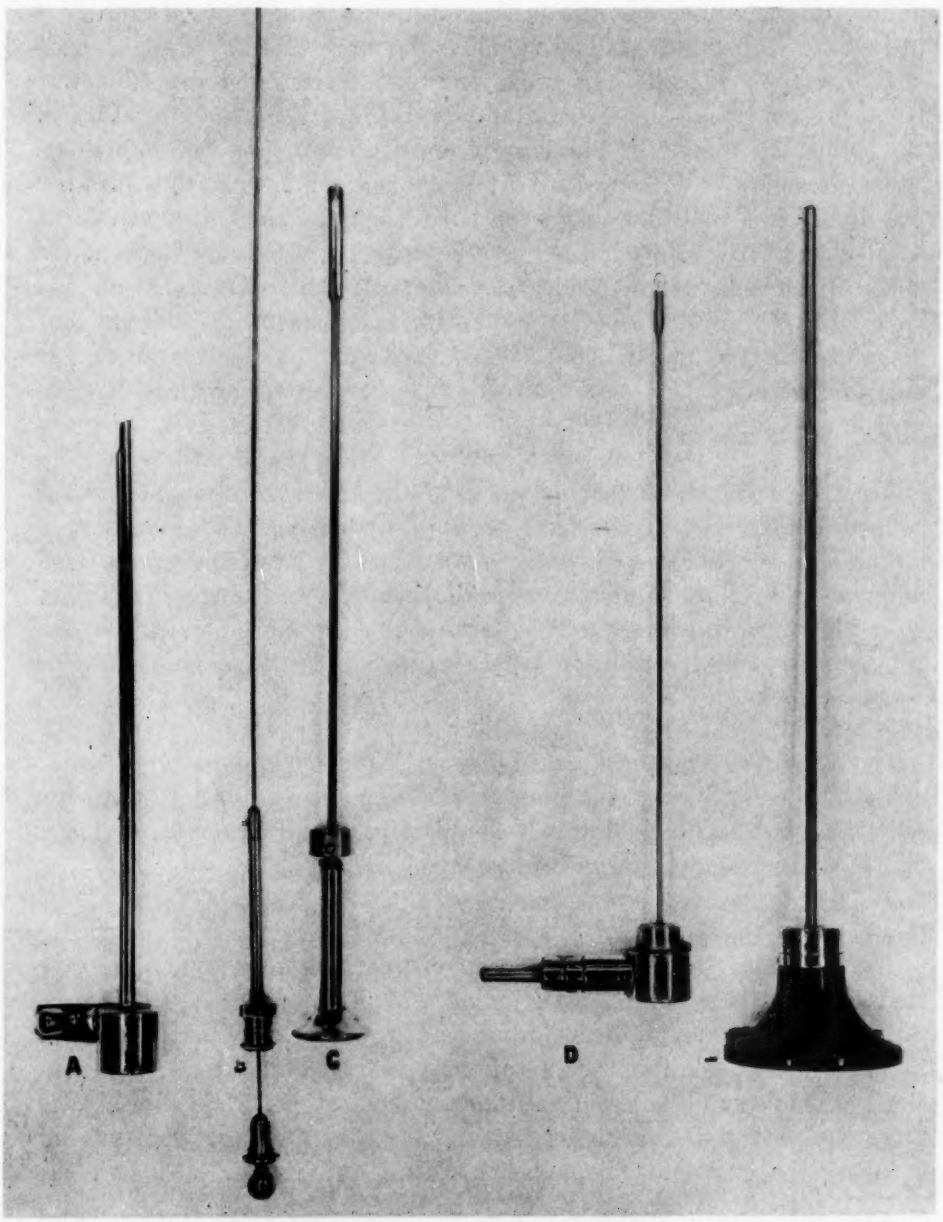

Fig. 2.—*A.* Cannula. *B.* Guide needle (stylet partly withdrawn). *C.* Obturator. *D.* Lighting system. *E.* Lens system with eyepiece.

in a rounded plug fitted with an electrode, thus furnishing contact with battery wires. An aperture in the center of this plug receives the lens system.

D. *Lens System.*—The viewing system (Fig. 2, *E*) consists of a thin metal tube sheathing a series of lenses which provide a universal focus. The intraspinal end of the lens system terminates in a small window, while the proximal or extraspinal end has a conventional eyepiece. Two lens systems are furnished, one of which encompasses the field of vision almost directly ahead of the instrument, while the other provides approximately a right-angle view. This is the more useful.

E. *Range of Vision.*—The range of vision varies from approximately 0.5 to 2.5 cm. from the lens window, being limited by the curvature of the spine, the degree of illumination, and the nature of the pathology. Structures close to the objective are magnified, while those at a distance are diminished in size, though the entire field remains in sharp focus at all times. By rotating the eyepiece, inspection of the subarachnoid space within an arc of 360 degrees may be readily accomplished. At times it is necessary to rotate the entire instrument until satisfactory visualization is obtained. The field of vision may be further altered or enlarged by advancing or withdrawing the lens system within the cannula.

STERILIZATION

All except the glass-bearing parts of the instrument, including the rubber-covered battery wire, are sterilized by boiling.

The lens and lighting systems are sterilized by immersion for fifteen minutes in a solution of cystan green* made by dissolving one tablet in a pint of warm water. The parts should be rinsed in sterile distilled water or saline solution before being used.

EQUIPMENT FOR MYELOSCOPY

The necessary equipment includes: myeloscope and battery; novocain solution; 2 c.c. syringe and hypodermic needle; small medicine glass for sterile saline solution (should it be required for irrigation); No. 11 scalpel blade; sterile drapes; sponges; sterile gloves.

TECHNIQUE OF MYELOSCOPY

The patient is arranged as for an ordinary lumbar puncture, save that the skin is prepared with iodine and alcohol over a wider area. Suitable drapes are applied, and a few drops of 1 per cent novocain injected into the skin at the site of the proposed puncture. Apprehensive patients should be given preliminary medication. It is advisable to place the patient in the sitting position, leaning well forward, instead of using the customary recumbent posture on the side, although the

*Cystan green tablets contain a phenylmercuric salt having a high germicidal value with low toxicity, and have proved completely satisfactory for sterilizing the myeloscope. They are made by Charles Killgore, Inc., New York, N. Y., and can be supplied by the American Cystoscope Makers, Inc., New York, N. Y.

latter may be used. The sitting position greatly facilitates midline insertion of the instrument, one of the most important factors of a successful myeloscopic examination. The greater hydrostatic distention of the arachnoid and dural envelopes in the sitting posture also facilitates introduction of the instrument into the subarachnoid space. Myeloscopy should not be attempted within four or five days after a lumbar puncture, as the postlumbar puncture escape of cerebrospinal fluid into the epidural space renders myeloscopy difficult.

When the patient has been prepared as described, a small vertical incision is made in the skin at the point of the proposed puncture with a No. 11 scalpel blade. This incision, not more than 2 to 3 mm. in length, should be continued through skin, subcutaneous tissue, and interspinous ligament for a total depth of 1 to 1.5 cm. in order to establish the proper *midline* pathway for insertion of the myeloscope.

Insertion is accomplished by advancing the cannula (Fig. 2, *A*), which has been previously fitted with the obturator (Fig. 2, *C*) and guide needle (Fig. 2, *B*), along the scalpel tract and then 1 to 2 cm. farther, so that the tip of the instrument comes to rest about two-thirds the distance from skin to dura mater (Fig. 3*A*). The guide needle (Fig 2, *B*) is now unlocked from its "neutral" position (indicated by the zero mark on its handle), and advanced ahead of the resting cannula until the dura mater and arachnoid membrane are penetrated (Fig. 3*B*). In doing this, two points of minor resistance are generally appreciated, one being caused by passage of the needle point through the ligamentum flavum, and the other by its passage through the dura mater. The stylet is then removed, whereupon cerebrospinal fluid flows out the needle. Manometric studies, if desired, should be carried out at this stage and specimens of cerebrospinal fluid obtained.

The precise distance from obturator tip to the subarachnoid space is now determined, by noting the distance the guide needle has been advanced. This distance is read from the millimeter calibration on the handle of the needle. The needle must now be restored to and locked in its original neutral position. The whole instrument (cannula with obturator and needle) is then advanced the required distance, by reference to the millimeter scale on the shaft of the cannula. The tip of the obturator should now have penetrated the dura mater and arachnoid, leaving the tip of the cannula just outside the dura (Fig. 3*C*).

The position of the instrument should be checked by withdrawing the stylet or the entire guide needle, where upon cerebrospinal fluid should flow freely. If no fluid is obtained, it may be necessary to advance the instrument another millimeter or two. It is helpful to realize that the penetration of the ligamentum flavum and of the dura mater can be appreciated by the sense of touch. It should also be remembered that a space-occupying lesion or deformity of the spine may prevent proper insertion of the instrument.

With the cannula properly placed, the obturator and guide needle are removed and replaced first with the electric light carrier (Fig. 2, *D*) and finally with the lens system (Fig. 2, *E*). These two parts of the apparatus should be introduced with gentleness. Generally the electric bulb tip will pass at once through the dural and arachnoid openings made by the obturator, as will the after-coming lens system, whereupon visualization of the cauda equina may be carried out (Fig. 3*D*).

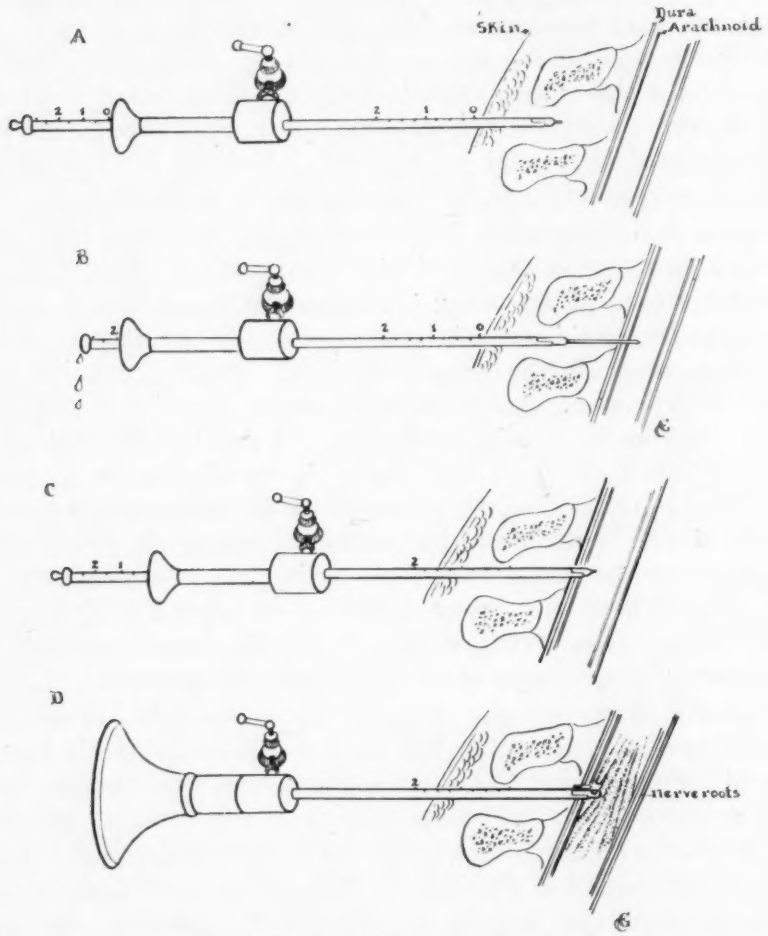

Fig. 3.—*A*. First step in introduction of myeloscope: Cannula with obturator and guide needle penetrating interspinous ligament. *B*. Second step: Guide needle advanced until cerebrospinal fluid is obtained. Millimeter scale on handle of needle then indicates distance from obturator tip to subarachnoid space. *C*. Third step: With guide needle returned to original neutral position, the entire instrument is advanced the required distance. *D*. Final step: Obturator and guide needle are replaced by lighting and by lens systems.

It is sometimes necessary to resort to further manipulation in order to achieve a satisfactory visualization. The bulb tip, for example, may not at first penetrate the dural aperture made by the obturator. In such a case one must rotate and advance the entire apparatus under direct vision, until the bulb tip has been inserted into the dural open-

ing, which can then be enlarged by gently tilting or rocking the whole apparatus. Should wisps of epidural fat or arachnoid membrane interfere with visualization, further advance or rotation of the lens system may be necessary until the lens has either passed the obstructing tissue, or brushed it aside. On rare occasions, it may be necessary to inject 2 to 3 c.c. of warm sterile saline solution through the adaptor, to clear the field of extravasated blood from an epidural vein.

Another difficulty in visualization may be due to the nature of the underlying pathology. A neoplasm or extruded intervertebral disk, for example, may so fill the spinal canal that attempts to advance the needle result in compression of the underlying nerve roots and hence cause pain. The occurrence of pain should therefore be regarded as a point of diagnostic significance and should lead the examiner to reinsert the myeloscope at a higher or lower level.

Before withdrawing the instrument one should always remove the lens system first, so that the light bulb will drop back into the lumen of the cannula. A sterile dressing should then be taped securely over the puncture site, and the patient treated as after any lumbar puncture. It is of interest to note that the incidence of postmyeloscopy headaches has been no higher than after an ordinary lumbar puncture despite the fact that considerable cerebrospinal fluid is sometimes lost.

APPEARANCE OF NORMAL STRUCTURES

The first tissue one ordinarily sees on advancing the lens system is epidural fat (Fig. 4*A*), which is loose, globular, and glistening in appearance, yellowish in color, and exhibits small blood vessels which course over and through its substance. It can hardly be mistaken for anything other than adipose tissue. Beyond the epidural fat lies the dura mater, which appears as a firm gray-white or slightly bluish, opaque membrane, vertically striated. If the myeloscope has been introduced lateral to the midline, a nerve root in its extradural course may be seen.

On passing the bulb and lens through the dura one visualizes the arachnoidea spinalis, which normally appears as a filmy, transparent membrane. The arachnoid membrane usually oscillates in harmony with the patient's respiratory excursions. The arachnoid membrane of the ventral aspect of the spinal canal has occasionally been visualized. On occasions, plaques[5] of calcification, incorporated within the ventral portion of the arachnoid, were seen by the myeloscope and later verified at operation.

Within the arachnoid membrane lie the nerve roots of the cauda equina. Those first encountered are of course the dorsal roots, of which the smallest and most centrally situated are the sacral roots, as contrasted with the larger lumbar roots in a more lateral position. All the nerves are normally quite straight in course and free to oscillate with

the respiratory excursions of the cerebrospinal fluid. The filum terminale (Fig. 4*B*, central vertical structure) appears as a rather loose, small, slightly sinuous structure having a bluish tinge in contrast to the gray-white color of the nerves. Close examination of the nerve roots discloses their longitudinal fasiculi. Along the surface of each root there run one or more fairly straight blood vessels.

The flow of blood may sometimes be seen, when the lens objective is sufficiently near a root to magnify its blood vessels. In such instances, arterial circulation (red) and venous flow (bluish) can be readily distinguished, the blood coursing in opposite directions in adjacent vessels on the same root. The direction of arterial flow is caudad. Arrest and even temporary reversal of flow can be recognized when the patient coughs or strains. The administration of amyl nitrite by inhalation has produced a visible dilatation of the vessels.

EXAMPLES OF PATHOLOGY VISUALIZED BY MYELOSCOPY

1. *Neuritis.*—A patient suffering from clinical neuritis of the left sciatic nerve, secondary to focal infection, was found on myeloscopy to have reddened, inflamed looking nerve roots on the left side of the cauda equina at L 4-5 (Fig. 4*B*). The vessels of the affected nerves were diffusely dilated in contrast to the normal nerves and vessels on the opposite side.

2. *Herniated Nucleus Pulposis.*—The effects of nerve root compression by a herniated nucleus pulposis can usually but not always be recognized by the myeloscope. A ventrally situated mass, resulting from an extruded "disk," has been seen clearly as shown in Fig. 4*C*. In this instance, the actual separation of nerve roots by the lesion was at once apparent, although clinical and x-ray studies had failed to reveal the site or nature of pathology. At operation, the herniated nucleus was successfully removed.

Fig. 4.—*A*. Normal structures (myeloscopic appearance) showing epidural fat on each side of the field, with extradural nerve root at left. The aperture in the dura (bluish) has been exaggerated for diagrammatic purposes. Crossing the upper angle of the dural opening is part of the arachnoid membrane, through which can be seen two nerve roots of the cauda equina and their blood vessels. The space between nerve roots usually appears dark, because in shadow.

B. Neuritis: Two inflamed nerve roots are seen at the left; the filum terminale in the center; and two normal roots at the right. A portion of the epidural fat and underlying dura mater can be seen at the lower third of the field, while at the extreme right is a bit of the arachnoid membrane.

C. Herniation of nucleus pulposis: The transverse, yellowish, ventrally situated mass represents part of an extruded intervertebral disk.

D. Herniation of nucleus pulposis: Myeloscopic appearance of similar lesion to that shown in *C*. In this case the mass itself was not seen owing to the extreme compression of the overlying nerve roots, which were broadened and discolored, as indicated at the lower portion of the field. The same roots presented a normal appearance at a higher level.

E. Hypertrophied ligamentum flavum (unilateral) which caused acute unilateral sciatica due to compression of a nerve root near its foramen of exit. The lesion itself was not visualized, but the greatly dilated and tortuous blood vessel of the second root from the left indicated pressure on that nerve at a lower level. (Myeloscopic findings verified at operation.)

F. Neuroepithelioma of cauda equina: Myeloscopic appearance of discrete neoplasm attached to a single nerve root. Note moderate tortuosity and dilatation of blood vessel on the nerve giving rise to the tumor.

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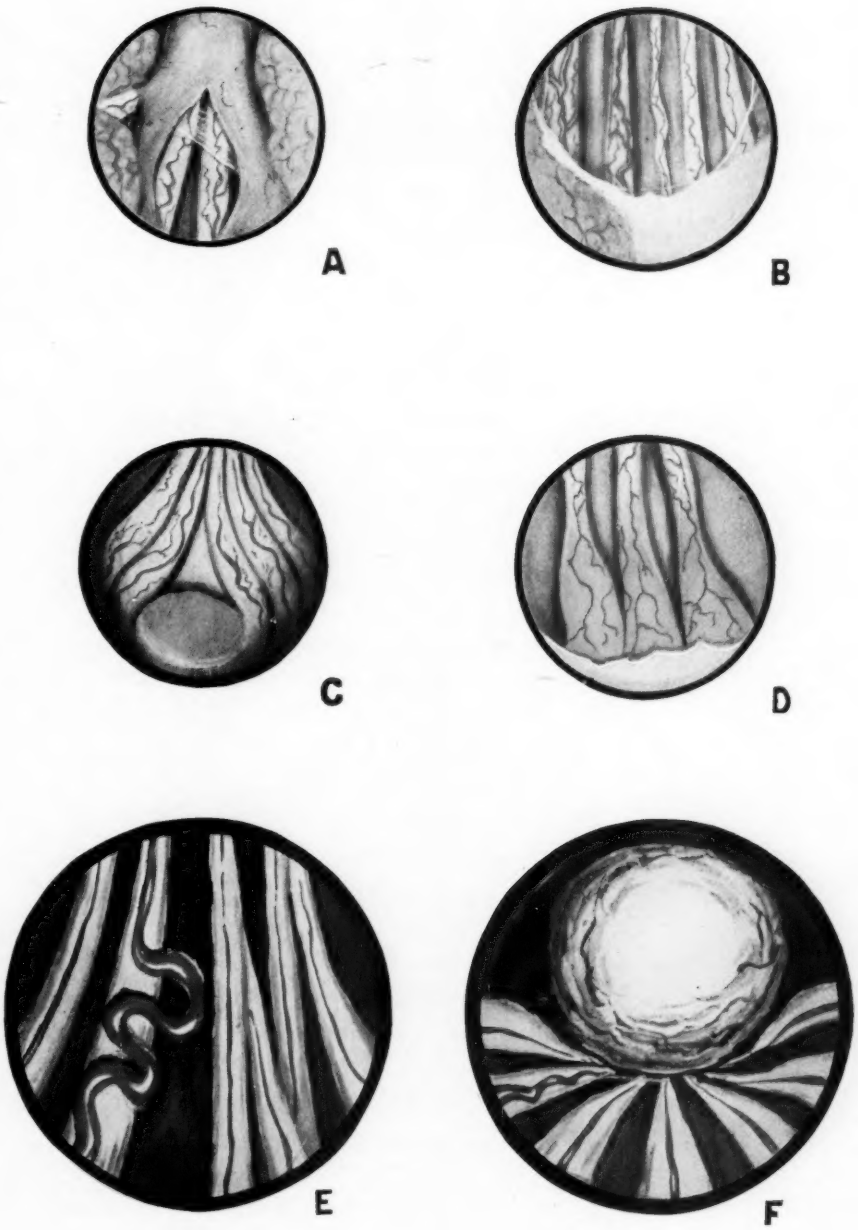

Fig. 4.—See opposite page for legend.

Another example of the effects of a ventral, transverse herniated nucleus pulposis is shown in Fig. 4*D*. In this case the mass itself was not visible, but the overlying nerves were plainly displaced in a dorsal direction, and appeared broadened as well as discolored. On rotating the eyepiece, the same nerves appeared quite normal at a slightly higher level, as indicated in the diagram.

Unilateral extrusions of the nucleus pulposis result in compression of roots on the affected side only, so that their edges appear close together in contrast to the normal separation and oscillation of the freer roots on the unaffected side. The nerves in the vicinity of such a mass often present an edematous appearance, and may have inter-rhizoid strands of arachnoid adhesions.

3. *Hypertrophied Ligamentum Flavum.*—The presence of a thickened ligament has frequently been detected by finding an unusually large epidural space, with secondary narrowing of the subarachnoid space. This condition can be appreciated in part by the difficulty of visualizing the cauda equina because of the limited intraspinal space; and in part by the sense of increased distance on passing the instrument through the ligamentum flavum (as described under the discussion of technique). It has also been possible, in a man suffering acute unilateral "sciatica," to recognize this lesion by the presence of a greatly distended, looped, root vessel, obviously due to compression of that nerve at a lower level (Fig. 4*E*). At operation a large wedge-shaped unilateral ligamentous mass was removed with immediate, lasting relief.

4. *Neoplastic Diseases, Primary.*—If myeloscopic examination is made directly over a large primary neoplasm such as a neurofibroma, meningioma, or ependymoma, one may be unable to visualize the tumor, owing to the cramped space, unless the examination is repeated at another level. When such a tumor is seen by close application of the lens window to the neoplasm, it appears as an amorphous lobulated, gelatinous yellow-brown tissue. Sometimes the delicate arachnoid-like membrane or capsule of the tumor, with its blood vessels, can be identified. On one occasion, when it was necessary because of pain to reinsert the myeloscope at a higher level, a discrete rounded mass was clearly distinguished, filling the spinal canal (Fig. 4*F*). At operation this proved to be an encapsulated neuroepithelioma, attached to the left second sacral dorsal root. The vessel on the root to which the tumor was attached appeared dilated and moderately tortuous.

Neoplastic Diseases, Metastatic.—Metastatic invasion of the lower spinal cord and its nerve roots from a cerebellar medulloblastoma is not infrequent. Myeloscopic examination at the level of L 1 in such a case revealed nerve roots which were so enlarged as to be tightly packed within the spinal canal; they were dull gray in color and edematous in appearance.[2] At autopsy several months later these findings were corroborated both macroscopically and microscopically.

Metastatic carcinoma involving one side of the fourth lumbar vertebra, in a patient with signs of nerve root compression at that level, has also been recognized by myeloscopy.[2]

Varicose Vessels.—The importance of recognizing varicose vessels of the cauda equina lies in the fact that such vascular abnormalities represent a similar condition affecting the spinal cord, for the blood supply of the cauda equina is continuous with that of the spinal cord. Varices may extend the entire length of the cord, or may be confined to a few segments thereof.[6] Myeloscopy is therefore indicated in patients having signs of diffuse or focal cord disease of obscure etiology, especially since x-ray treatment is often beneficial in cases of varices.

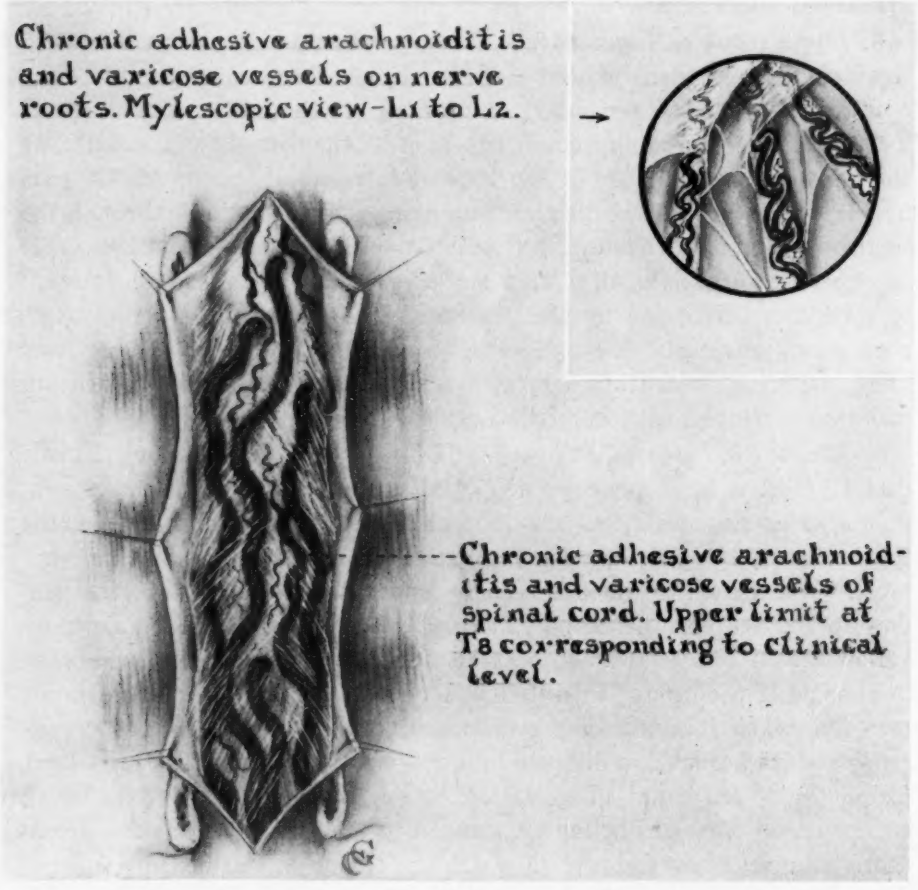
Chronic adhesive arachnoiditis and varicose vessels on nerve roots. Mylescopic view-L1 to L2.
Chronic adhesive arachnoiditis and varicose vessels of spinal cord. Upper limit at T8 corresponding to clinical level.

Fig. 5.—Varicose vessels of cauda equina and spinal cord with associated arachnoid adhesions: The two conditions are not necessarily coexistent. Inset shows myeloscopic appearance (upper right) while appearance at laminectomy is indicated at left. This represents the post-traumatic acquired type of varicosity, distinguished by the fact that the intrinsic vessels of the nerve roots are abnormally large and tortuous.

There appear to be two main categories of spinal varices, one congenital, the other acquired. There is sometimes an associated chronic adhesive arachnoiditis with the latter type, as indicated in Fig. 5. The characteristic features of both types of spinal varices are the enlargement and the extreme tortuosity of the involved vessels. In a given

case, both arterial and venous channels may participate in the process, and the vessels in any one case may vary in degree of dilatation and corkscrew appearance.

The congenital type of varicosity generally manifests itself in young individuals during their first two decades, and is distinguished by the fact that the abnormal vessels within the lumbar canal (where they are visualized by the myeloscope) are *separate from* the nerves (Fig. 6); while the acquired type of varix, occurring in older individuals, is in general represented by dilatation and tortuosity of the vessels *on the nerves* (Fig. 5). Careful comparison of Figs. 5 and 6 will make this point clear.

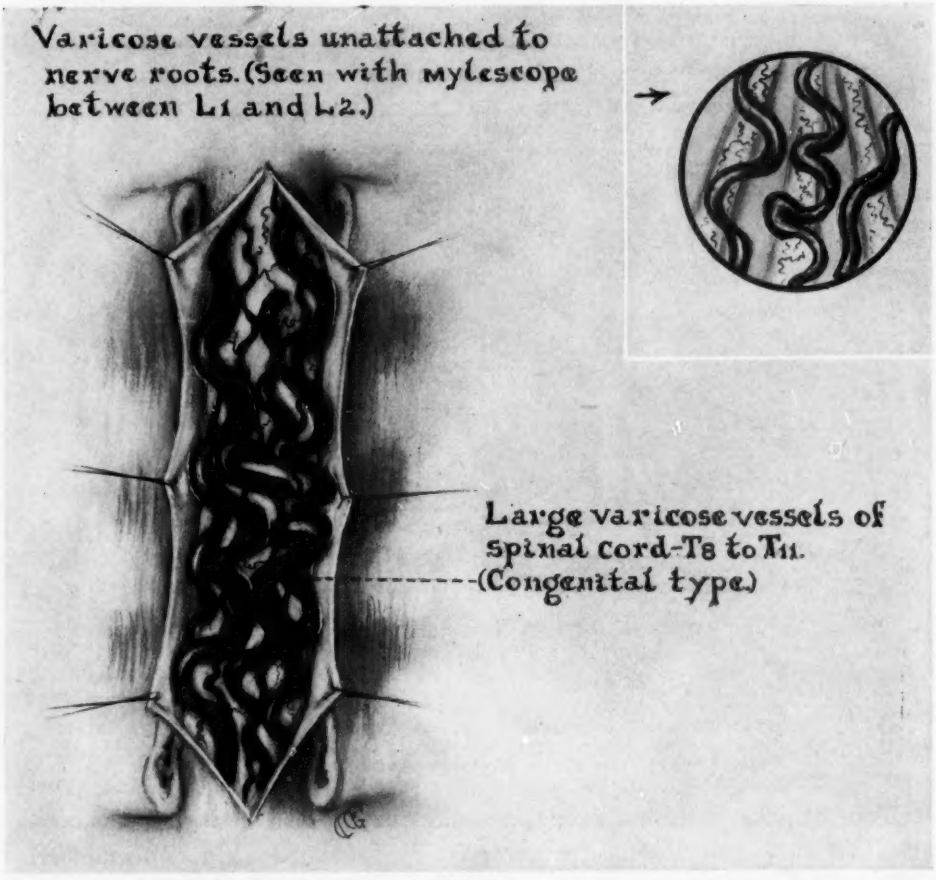
Varicose vessels unattached to nerve roots. (Seen with mylescope between L1 and L2.)
Large varicose vessels of spinal cord-T8 to T11. (Congenital type.)

Fig. 6.—Varicose vessels of cauda equina and spinal cord of congenital type. Note that in this condition, which resembles an hemangioma, the varicose channels are separate from the nerve roots.

The congenital varicosity therefore resembles an hemangioma; whereas, the second (acquired) type of varix suggests slowly progressive dilatation of the intrinsic blood supply of spinal cord and cauda equina. In many instances, though not always, the latter type appears to have been the result of trauma. This belief is expressed because many patients suffering from this condition give a history of oft-repeated

jarring trauma, such as from falls off a horse. This view is further substantiated by my experience in exposing the spinal cord of patients who have had some form of focal injury to the cord (such as a severe blow, or an adjacent stab wound). In such cases, varicose vessels often penetrate the substance of the cord at the level of trauma. Usually these abnormal vessels course caudally for a considerable distance, thus explaining their presence on the nerve roots of the cauda equina. There are three possible explanations of post-traumatic varices, which may act alone or in combination to produce the vascular pathology: (1) gliosis of the cord; (2) constrictive arachnoiditis around the cord; (3) traumatic insult to the vessels themselves.

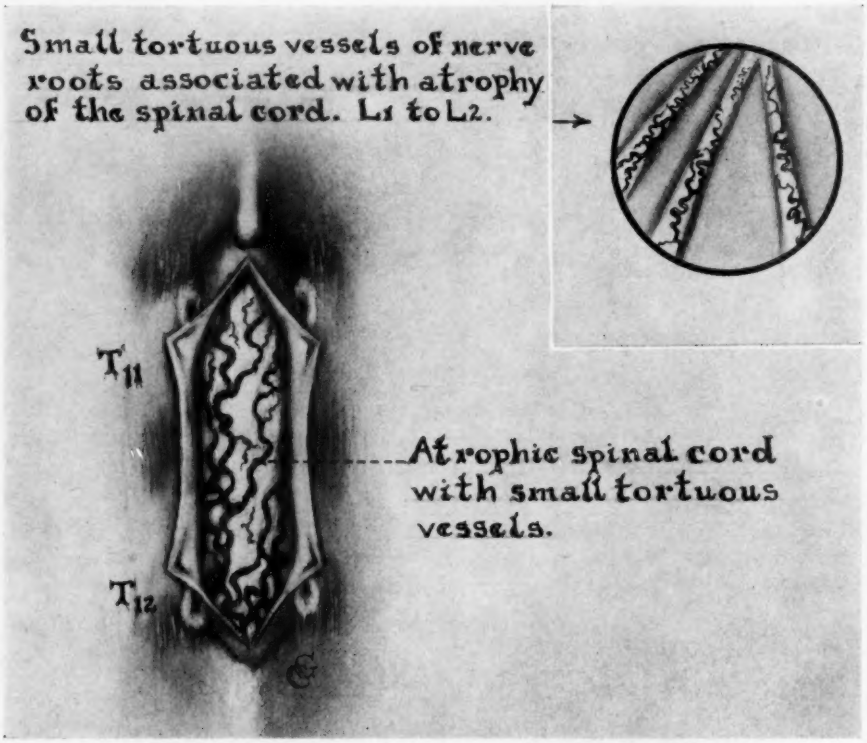
Small tortuous vessels of nerve roots associated with atrophy of the spinal cord. L1 to L2.
T11
T12
Atrophic spinal cord with small tortuous vessels.

Fig. 7.—Arteriosclerosis of cauda equina and spinal cord.

Two other conditions sometimes associated with acquired varicosities are (1) arteriosclerotic atrophy of the cord (Fig. 7) and (2) intramedullary tumor of the cord. The differential diagnosis, in the final analysis, must be made by weighing every factor in a case, including history, clinical findings, course, and laboratory aids, with special reference to manometric and total protein studies.

Arachnoid Adhesions.—This condition can be recognized by the presence of filmy adhesions not only between the nerve roots but also between roots and the arachnoid membrane. The adhesions often resemble cobwebs scattered irregularly among the nerves, as shown in Fig. 6. They may appear as delicate strands, or as hourglass or triangular

sheets.[2] In certain cases the nerve roots appear glued together by the adhesive process. The arachnoid membrane itself is usually thickened and translucent, instead of being tenuous and transparent; while the nerve roots, instead of being freely movable, are firmly fixed. Patients who suffer from this process generally give a history of antecedent infection or trauma, and may have symptoms and signs of diffuse spinal cord disease.[7] On several occasions, patients long suspected of post-traumatic malingering have been found by myeloscopy to harbor dense, localized adhesions on one or both sides of their cauda equina.

Operative mediation is often of value in cases of adhesive arachnoiditis, and may prevent the onset of syringomyelic cavities within the cord.[7, 8]

Inflammatory Conditions of the Leptomeninges.—When myeloscopy reveals the presence of an amorphous epidural mass, with many small blood vessels, such lesions at operation have proved to be granulomas, some associated with syphilis, others with an arrested tuberculous process, and still others of unknown etiology. Sometimes the granuloma may lie at some distance from the inflammatory reaction observed through the myeloscope.

Lipiodosis.—The term lipiodosis has been coined to describe the presence of subarachnoid droplets of lipiodol, following previous introduction of this oil. The lipiodol appears as tiny golden globules clinging tangentially to the nerve roots like particles of honey.

Gas Myelography Through Myeloscope.—Oxygen or air can be introduced into the subarachnoid space through the adapter on the side of the myeloscope after visualization has been completed. The technique differs in no way from the usual manner of performing gas myelography.

AFTEREFFECTS OF MYELOSCOPY

Despite the loss of from 5 to 15 c.c. of cerebrospinal fluid during myeloscopy, there has been no greater incidence of postpuncture headache than after an ordinary lumbar puncture. The reason may lie in the fact that the procedure is carried out with the patient in the upright position, so that intracranial dynamics accommodate themselves pari-passu with the outflow of spinal fluid. In this connection, it is of interest to note that the myeloscope has frequently revealed large collections of epidural fluid when an ordinary lumbar puncture has been done within the previous two to four days. This demonstrates that leakage of spinal fluid can continue for some time after an ordinary lumbar tap.[9] It is therefore wise to delay myeloscopic examinations for at least five days after a lumbar puncture has been done; otherwise myeloscopy may be difficult, since the dural and arachnoid envelopes will have lost their usual hydrostatic tension owing to the leak.

It has not yet seemed expedient to perform a myeloscopic examination over the spinal cord, although it has been carried out successfully within the cisterna magna of an anesthetized dog. It may be of further interest to note that the myeloscope has been used for intraventricular visualization through trephine openings in the human skull, and that attempts are now in progress to study action currents from the nerve roots of the cauda equina, through the myeloscope.

SUMMARY

1. *Myeloscopy.*—Diagnostic visualization of the cauda equina through a spinal endoscope called the myeloscope. Myeloscopy is usually performed under local anesthesia with the patient in the sitting posture, and is carried out in much the same manner as an ordinary lumbar puncture. Specimens of cerebrospinal fluid may be collected, manometric studies may be done, and gas myelography may be performed, through the myeloscope. Nearly 400 myeloscopic examinations have been made during the last four years.

2. *Value of Myeloscopy.*—

a. Differential diagnosis may be made between operable and inoperable lesions of the cauda equina (and lower spinal cord).

b. Post-traumatic malingering may often be ruled out by this means.

c. Many a patient can be spared lipiodol injection and even an exploratory laminectomy, by preliminary myeloscopy.

3. *Operable Conditions Diagnosed by Myeloscopy.*—Herniation of nucleus pulposis; hypertrophied ligamentum flavum; chronic adhesive arachnoiditis (post-traumatic or postinflammatory); granulomas; benign tumors; lipiodosis.

4. *Inoperable Conditions.*—Varicose vessels of various types (see text); arteriosclerosis of spinal cord; metastatic neoplasms.

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FRACTURES OF THE MAXILLA

Describing a Simplified Appliance for Craniomaxillary Support and Fixation

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FRACTURES of the upper jaw are of three general types: (1) Those involving a section of the jaw to include the alveolar process alone without a severance or displacement of the remaining portions of the jaw. Such a segment may be impacted into the remaining portions of the jaw and present displacement without mobility. These forms of process fractures may be combined with the second or third type of fracture. (2) Fractures of half of the upper jaw, the remaining half of the upper jaw being intact. These unilateral fractures may or may not show considerable mobility and present various types and degrees of displacement, impaction, or over-riding. (3) Complete fracture of the major portion of the upper jaw on both sides. Occasionally in horizontal fractures a portion of one tuberosity carrying a molar tooth may remain in solid continuity with the other bones of the skull. These fractures usually show mobility and displacement. They may, however, present an open bite anteriorly with the anterior portion slightly moveable; whereas, the posterior portion, the molar region, resists upward replacement to its proper occlusal level.

In the horizontal plane the fracture lines may extend through (1) the alveolar process or root-end level; (2) the midmaxillary sinus region; (3) the malar-orbit-ethmoidal level. In this latter group, danger of intracranial complication is present, and it may be wise to delay reduction of the fractures for several days in order to guard against infection and extension to the meninges.

It must be remembered that fracture lines disregard anatomic boundaries, and therefore fractures of the upper jaw of necessity must include all of the bones of the face with the exception of the frontal bone and the mandible. Consequently, they include fractures of the malar bones, lachrimal bones, the lateral masses of the ethmoid, and parts of the sphenoid.

Frequently the displacement produces a degree of malocclusion which makes it impossible to visualize the occlusion as it was before the accident. Study casts therefore should be made of the upper and lower teeth in most cases in order to determine the degree of displacement and rotation, and to make possible a more accurate application of the methods used to correct the displacement.

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The possibility of improving a previous malocclusion must always be kept in mind. We have been able to do this in several cases during the past few years.

It should be noted that roentgenograms of fractures of the maxilla are often most unsatisfactory and one must rely upon the clinical findings and more particularly, on a study of the occlusion of the teeth in the making of the diagnosis. It is therefore unnecessary to rush patients with severe upper facial injuries to the x-ray room and submit them to the discomfort of the manipulations necessary in taking a number of films of the facial region. A limited number of carefully positioned films including dental films may be taken at a later date should it be found that complete reduction of the fracture is not accomplished by the initial treatment.

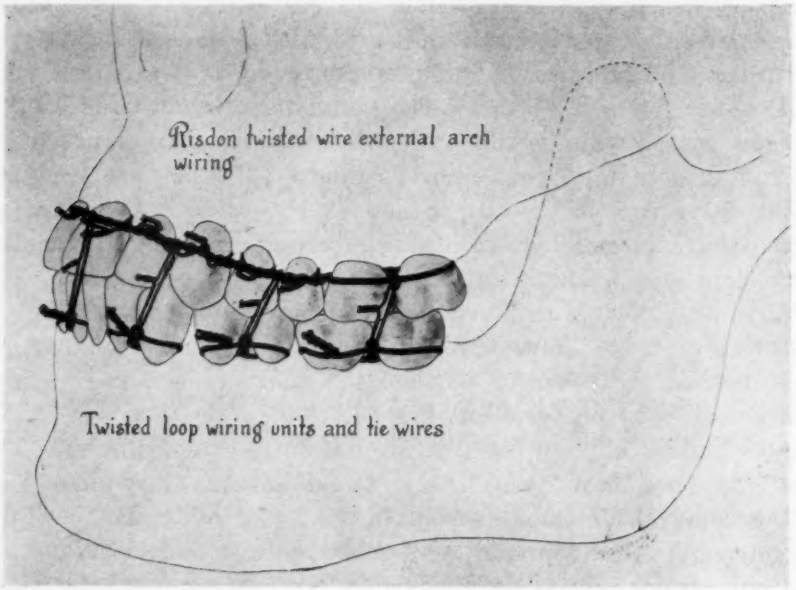

Fig. 1.—Teeth wired securely in occlusion by interdental wiring. In most cases of fractures of the upper jaw the essential treatment is the wiring of the teeth in correct occlusion after displacements have been corrected manually or by the use of diagonal tie wires or rubber-binder traction. When there is marked mobility of the entire upper jaw, this interdental wiring must be supplemented by external bandaging for a week or more.

Fractures of the alveolar process may involve the outer or inner table with the associated teeth, and the displacement may be labial, buccal, or lingual. In other cases, complete sections of the alveolar process containing the teeth may be torn loose from the body of the bone, in which case the mucoperiosteum will usually supply sufficient blood supply to maintain the vitality of the fragment.

As already noted, segments of the alveolar process may present varying degrees of mobility and may be either in a reasonably correct position or be considerably displaced. In all such fractures including the impacted fractures, it is necessary to make a careful diagnosis of the

dental condition of both jaws or at least the upper jaw before fully determining the procedure to be instituted. Displaced fragments should be replaced in correct position and occlusion as accurately as possible and retained by wiring or some dental appliance. In certain impacted fractures without much displacement, it is often wise to leave the fragment in its impacted position, particularly when it is obvious that future dental treatment would necessitate the removal of the teeth in the fragment in order to make the best possible dental restoration under the circumstances.

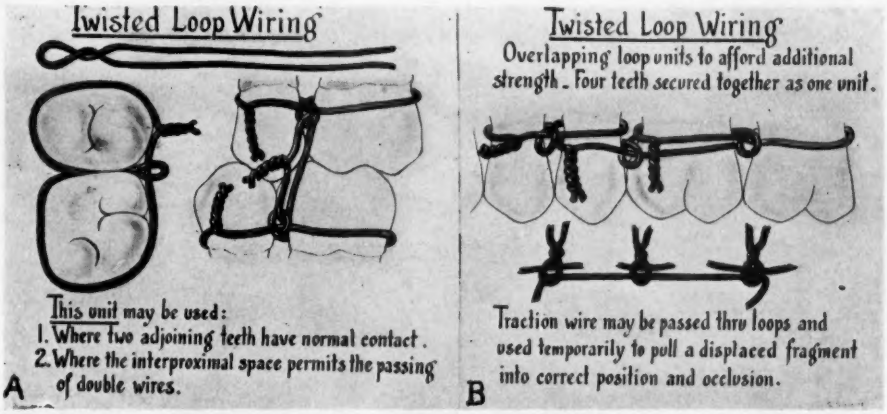
Twisted Loop Wiring
This unit may be used:
1. Where two adjoining teeth have normal contact.
2. Where the interproximal space permits the passing of double wires.
A
Twisted Loop Wiring
Overlapping loop units to afford additional strength. Four teeth secured together as one unit.
Traction wire may be passed thru loops and used temporarily to pull a displaced fragment into correct position and occlusion.
B

Fig. 2.—*A*. Twisted loop unit wiring (Ivy) is a very useful method by which the lower teeth may be secured to the upper teeth in occlusion by means of tie wires. *B*. Two or more loop units may be applied to overlap and secure three, four, or five adjoining teeth to provide additional strength. This is frequently necessary when strong wiring on the uninjured side of the jaw is used to elevate a fractured half of the upper jaw on the opposite side.

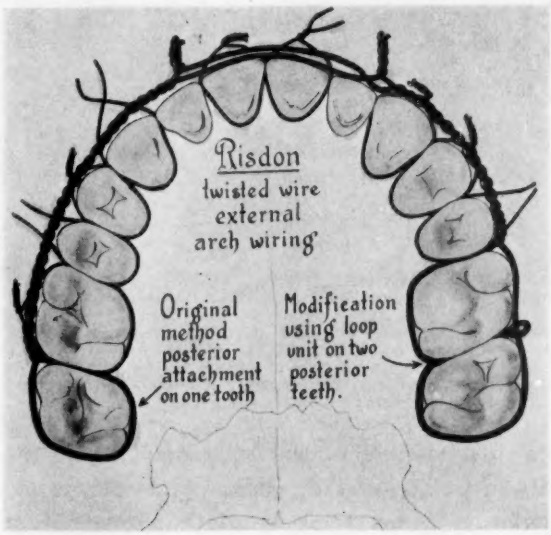

Fig. 3.—Risdon twisted wire external arch wiring is a very efficient and easily applied method of direct dental fixation to maintain two or more fragments in proper relation. Tie wires are used from the Risdon arch wire to similar arch wires or loop units on the teeth of the opposing jaw to secure the teeth in occlusion (see Fig. 1). This method has the distinct advantage that direct dental fracture fixation may be maintained after the tie wires are removed and the patient is permitted to open the mouth.

Fractures of half of the upper jaw with mobility can usually be nearly, if not completely, reduced by manipulation. In most cases, they should be maintained in correct occlusion by means of firm wiring of the teeth in occlusion on the uninjured side (Fig. 1). Two or three days of adjusting and tightening of the tie wires may be required to secure the teeth of the fractured side in good occlusion. For this purpose where considerable force is necessary, overlapping loop wiring is of great service (Fig. 2B). In addition to the wiring of the upper teeth to the lower jaw, the wiring together of the teeth on either side of the fracture may be indicated to give a finer adjustment of the ends of the fragments and to secure a more normal contact point (Fig. 3).

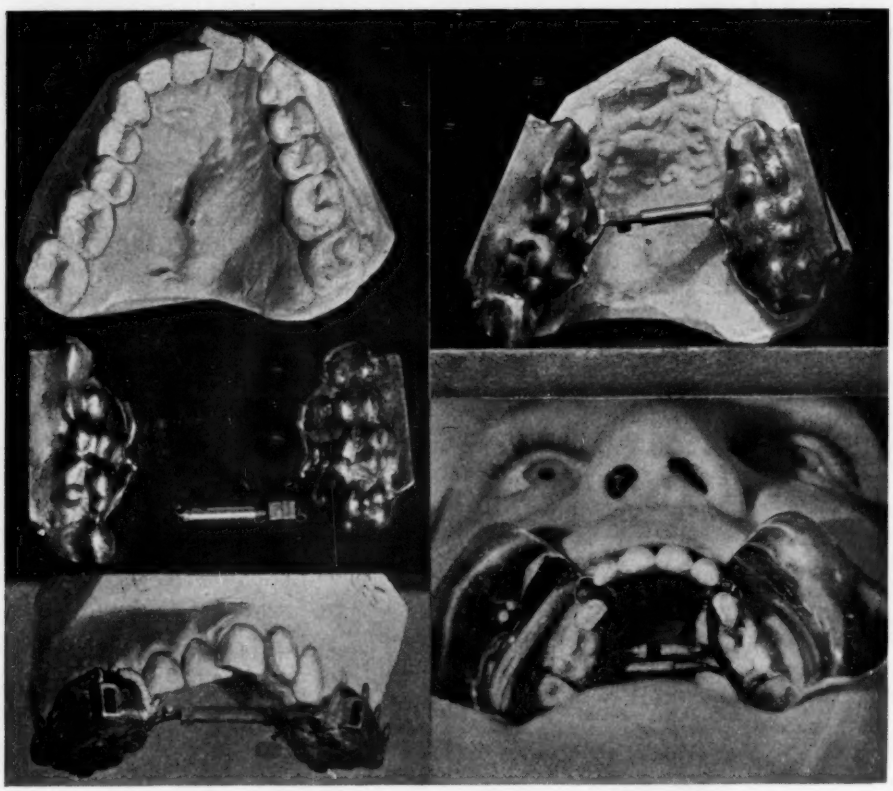

Fig. 4.—Jack screw splints may be used to push a fragment of the maxilla laterally to correct an over-riding at the midpalatal line. This type of splint may also be used to pull separated halves of the upper jaw together in the midline. Rectangular tubing soldered on the buccal sides of the splints may be used with extraoral arms to hold the entire upper jaw in its proper position (see Figs. 7 and 8).

There may be an over-riding of the bony margins of the fragments in the midline of the palate and an attempt should be made to correct this by manipulation before the mouth is closed in occlusion. For this a jackscrew splint may be necessary (Fig. 4). At times this over-riding with a permanent ridge must be accepted. In such cases, although the teeth may be in a useful occlusion, there will likely be a slight depression with flattening of the face on the affected side. It is usually necessary to keep the teeth wired in occlusion for a period of

three or four weeks following which the mouth may be opened, and the patient allowed to partake of more solid, but yet a fairly soft, diet. The complete and solid union of fractures of the upper jaw is usually slow in cases where the initial mobility has been great. It is frequently possible to note a definite spring or slight movement of the fractured side for three or four months after the injury. In time, however, union becomes clinically quite firm, and the patient is not conscious of any spring on strong mastication. For many months the teeth on the affected side may feel prominent or numb. There will usually be recovery from these symptoms or they may become hardly noticeable.

Unilateral fractures of the upper jaw may result in separation of the two halves of the jaw at the midpalatal suture line. These may prove to be difficult to approximate by the usual methods of wiring the teeth in occlusion and at times a special appliance must be constructed across the palate to use a jack screw to pull the displaced fragment into correct relationship with the uninjured side (Fig. 4). Rubber binder traction across the palate has been employed for the same purpose.

Complete fractures of the upper jaw show a wide variety of displacements according to the direction of the lines of fracture and the horizontal levels of the severance of the jaw from the deeper structures. At times, the jaw will be found mobile and subject to correction of the occlusion with but little manipulation. In a larger number of cases, the jaw is depressed and rotated, and in some instances, the entire maxilla is driven back to contact the posterior pharyngeal wall. The malar bone may also be fractured and driven down to become impacted into the displaced maxilla in such a way that the upper jaw cannot be manipulated or otherwise brought to its correct position and occlusion until the malar bone has been pulled outward and upward to its proper level.

At times, displacement may be very marked, particularly where there is depression of the molar region with open bite anteriorly, and replacement by manipulation and wiring is impossible. In such cases, a head appliance making possible the application of craniomaxillary force is indicated.

Many types of appliances have been devised to hold the fractured maxilla in its correct position by means of plaster of Paris headcaps to which are attached straps and metal arms, or by wire sutures which pass through the tissues of the cheeks. These in turn are attached to the fractured upper jaw by means of some form of dental splint or external arch bar appliance. It is obvious that methods employing straps or wire sutures can be efficient only when a strong upward or slightly diagonal pull will hold the fractured maxilla in its correct position. The extreme violence of present-day automobile accidents may result in a great deal of comminution of the thin walls of the maxilla. In such cases, any method that depends upon vertical and

diagonal traction in order to immobilize the fracture may elevate the maxilla to a higher level than normal before the parts are held securely. Union of the fracture then ensues with the occlusion of the teeth at a higher horizontal level than before the accident with a resulting

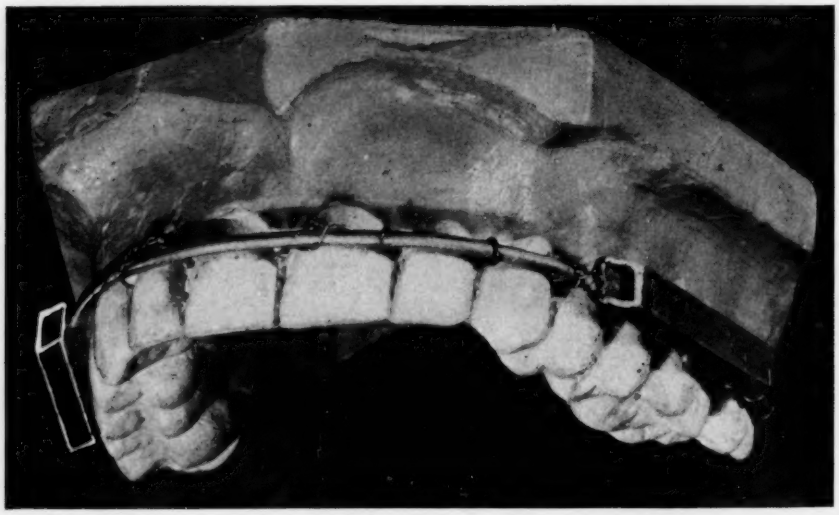

Fig. 5.—Universal upper jaw splint consisting of an arch bar to which is soldered rectangular tubing on each side in the bicuspid molar region. Several splints of various sizes should be constructed and kept on hand. The splint is secured to the upper teeth by wiring.

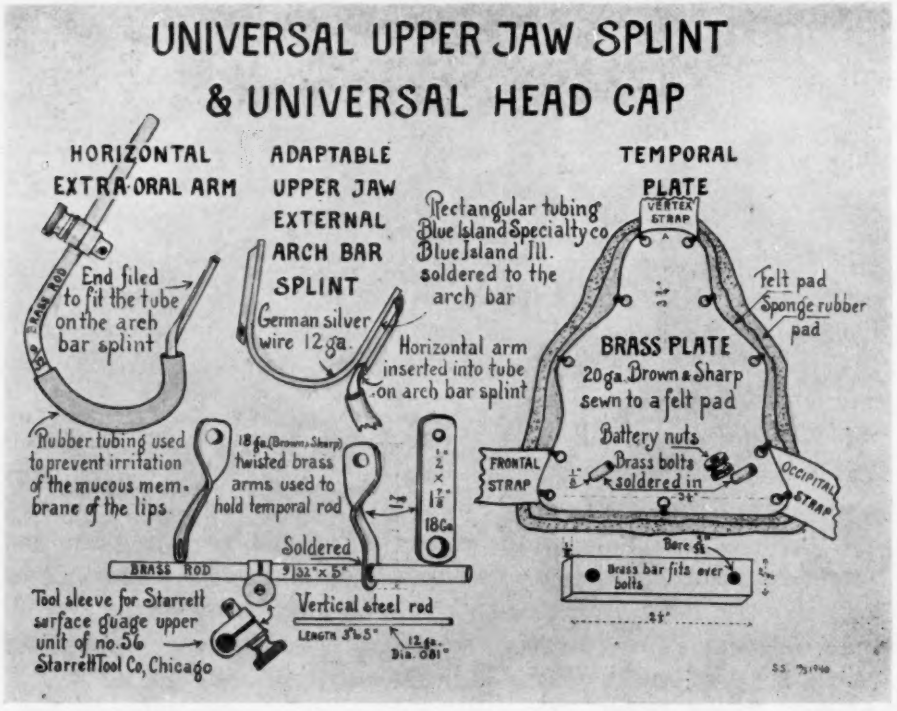
UNIVERSAL UPPER JAW SPLINT
& UNIVERSAL HEAD CAP
HORIZONTAL EXTRA-ORAL ARM
ADAPTABLE UPPER JAW EXTERNAL ARCH BAR SPLINT
TEMPORAL PLATE
End filed to fit the tube on the arch bar splint
Rectangular tubing Blue Island Specialty co Blue Island Ill. soldered to the arch bar
German silver wire 12 ga.
Horizontal arm inserted into tube on arch bar splint
Rubber tubing used to prevent irritation of the mucous membrane of the lips.
18 ga. (Brown & Sharp) twisted brass arms used to hold temporal rod
Soldered
BRASS ROD
Tool sleeve for Starrett surface guage upper unit of no. 56 Starrett Tool Co, Chicago
Vertical steel rod
LENGTH 3 1/2 to 5"
12 ga. Dia. .081"
VERTEX STRAP
Felt pad
Sponge rubber pad
BRASS PLATE
20 ga. Brown & Sharp sewn to a felt pad
Battery nuts
Brass bolts soldered in
FRONTAL STRAP
OCCIPITAL STRAP
Brass bar fits over bolts

Fig. 6.—Detailed assembly of materials used in the construction of a universal head-cap.

closure of the bite and probably subsequent development of traumatic changes in the temporomandibular joints. We have seen several cases of this type. Furthermore, traction straps or suspension wires do not afford adequate lateral traction or permit the application of lateral pressure upon a displaced maxilla. To overcome these faults of the appliance we began using a steel vertical extraoral arm which slips into rectangular tubing on an upper dental splint, and extends forward between the lips and then upward to be attached to a temporal plate on the headcap. This method provides efficient fixation of the jaw in all directions, but in practice it was often found difficult to bend and adjust the extraoral arm satisfactorily. Repeated removal for bending and adjustment of the arm was time-consuming and annoying to both

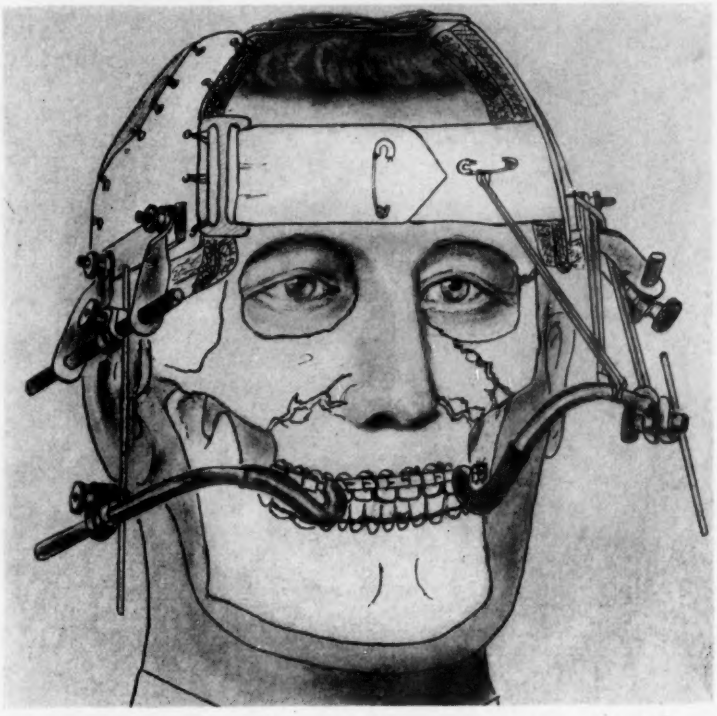

Fig. 7.—Universal upper jaw splint and headcap appliance, anterior view.

patient and surgeon. About ten years ago we discovered a type of universal joint that greatly simplified the many problems previously found so troublesome in the treatment of these cases. It permits adjustment of the displacement in all directions and planes and when tightened is most secure.*

Instead of a vertical extraoral arm, we now use a horizontal arm, the end of which slips into the rectangular tubing on the arch bar maxillary dental splint (Fig. 5). The horizontal arm is a standard

*This universal joint is a standard tool appliance made by the Starrett Tool Co., Chicago, Ill., the tool sleeves of the upper unit of No. 56 Starrett surface gauge.

brass rod 9/32 inch in diameter which fits the universal joint. A vertical steel rod, 12 gauge diameter, 0.081 inch, fits the universal joint and extends to a second universal joint on the brass rod of the temporal appliance to complete the fixation of the parts. We have from time to time simplified this headcap appliance. The present assembly is shown in Figs. 6 and 7. All metal materials may be obtained through hardware companies and the complete appliance may be constructed without difficulty by any good workman.

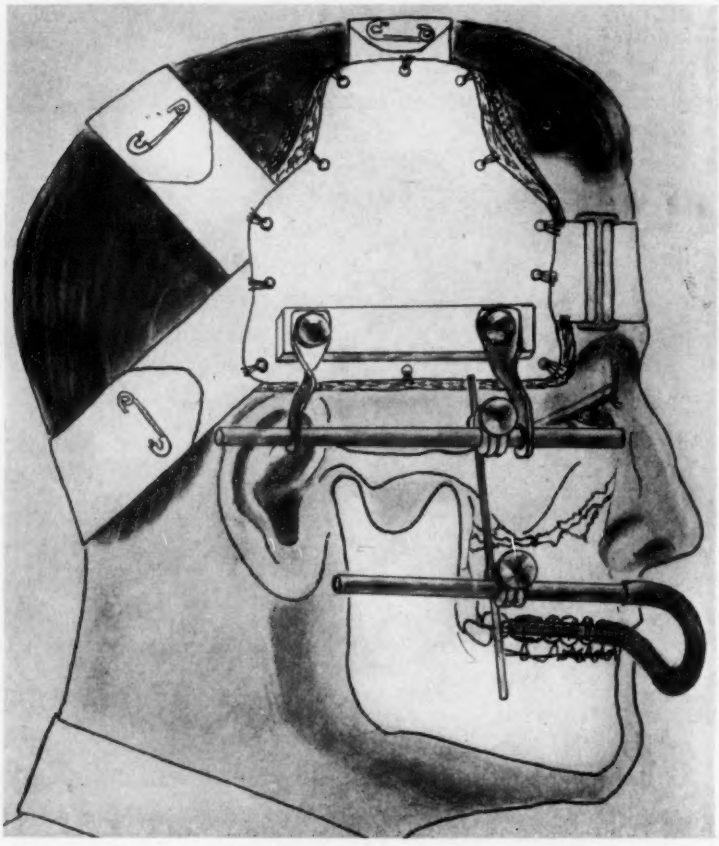

Fig. 8.—Right lateral view of appliances showing the routine immobilization of the fractured maxilla to the universal headcap.

The head appliance has been simplified and made more of the skeleton type by means of strong, adjustable cotton bands securely sewn to the temporal pads and plates (Fig. 7). These afford a more stable hold upon the occipital and frontal regions, thus overcoming the tendency of the head appliance to slip forward when considerable force is necessary to elevate and hold the fractured upper jaw. This forward slipping is an annoying and troublesome characteristic of the orthopedic plaster headcap made of stockinet, harness felt, temporal head plates, and plaster of Paris bandages which we formerly used. In markedly crushed and comminuted fractures it has been considered necessary to

try to maintain a proper horizontal occlusal level by wearing such an appliance for six or eight weeks.

It is often most difficult to reduce completely maxillary displacement at the first attempt and manipulations over a period of two or three days may be necessary to correct completely the displacement and restore normal occlusion. The universal joints facilitate the reduction in these difficult cases. It must be stressed that early correction of displacements is very important in the treatment of fractures of the maxilla.

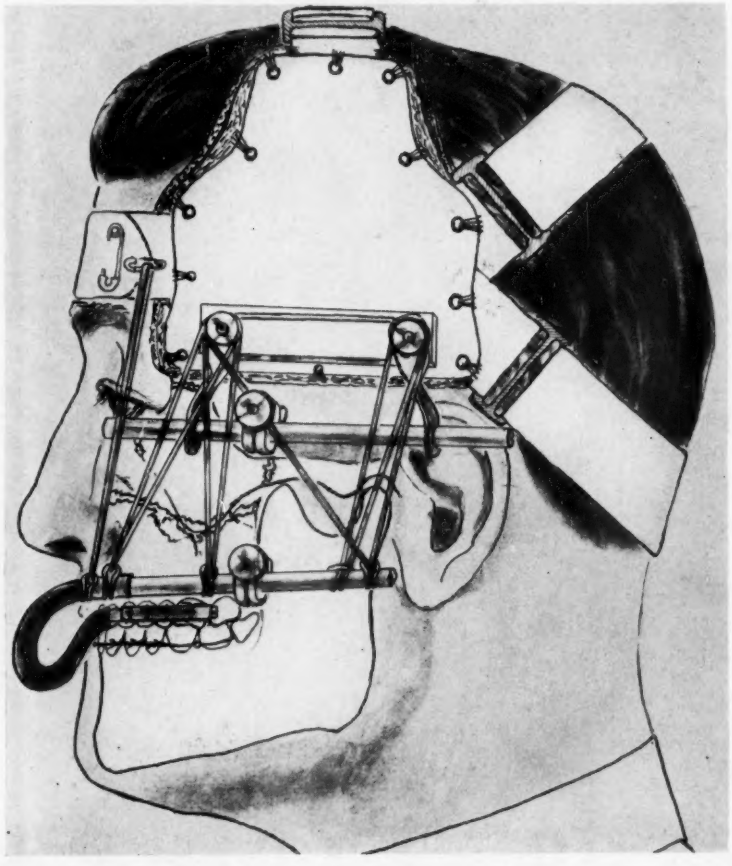

Fig. 9.—Left lateral view showing the temporary use of rubber binder traction for the elevation of a depressed maxilla. Diagonal traction may be secured and an oblique or direct outward pull may be obtained from the horizontal extraoral arm to one or two vertical rods attached to the temporal rod as shown in Fig. 10.

In cases with marked lateral displacement, we have on several occasions used on one side a regular extraoral arm (Fig. 8) and on the other inserted a horizontal extraoral arm which is utilized for the attachment of rubber binders running to the temporal headplate rod or bolts (Fig. 9). By adjusting these binders and the arm, considerable pull can be exerted in an upward and outward direction. Marked resistance to replacement has succumbed to this continual force over a

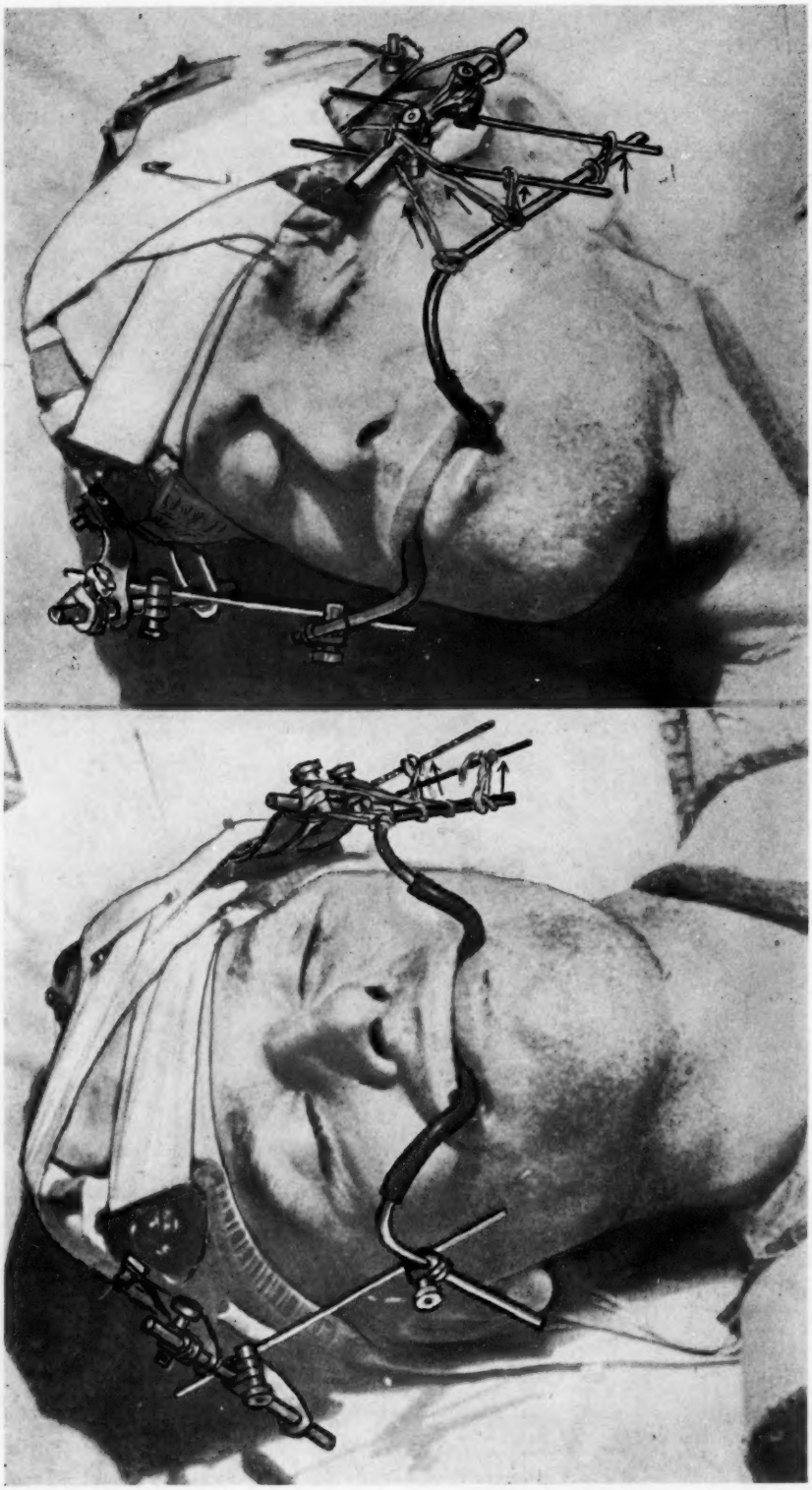

Fig. 10.—Retouched photographs of patient with universal upper jaw splint and headcap appliance showing routine assembly of horizontal arm—vertical rod and temporal rod on the right side of the face. Rubber-binder traction is used to elevate the left side of the maxilla and lateral traction is secured by rubber binders from the horizontal arm to vertical rods to move the maxilla to the left.

period of twenty-four hours. At this time, the teeth may be wired together by the loop method of indirect dental fixation or the splint may be used further and a vertical rod attached to the horizontal arm, discontinuing the rubber binders. In practice, the emergency headcap is reinforced and made to fit more securely by means of several strips of adhesive tape or by ace bandage (Fig. 10).

Except in extremely complicated cases with loss of many teeth and lack of occluding teeth in the mandible, the head appliances may be dispensed with in a week or so and the teeth wired in occlusion in order to obtain a finer adjustment of the occlusion and a better ultimate result. If there should be a tendency for the mandible to move and displace the maxilla, additional support by bandaging from chin to vertex is necessary. This is much more desirable and comfortable than the wearing of a plaster headcap maxillary appliance for five to eight weeks as recommended by many authors. The great adaptability of the universal joints appliance makes it possible to dispense with the headcap appliance and horizontal arm at the earliest possible time. Should occasion arise, it may be quickly reapplied without difficulty. After four to six weeks have elapsed, the tie wires may be cut and the patient allowed to open the mouth and eat soft food. Very slight mobility of the maxilla may be demonstrated for several months, but in most cases, displacement does not recur.

Associated fractures of the lower jaw, particularly if multiple and badly displaced, present great problems in the successful handling of the cases. They tax the ingenuity of the surgeon, for new methods and appliances must be devised from time to time.

Fractures of the upper jaw that have united firmly in malposition produce a serious and handicapping malocclusion of the teeth. Many factors must be considered before determining the plan of treatment that should be followed. The age and condition of the patient together with the absence of several teeth or the loosening or root-end infection of a number of teeth may indicate that extraction of all of the remaining upper teeth and the construction of an upper denture to re-establish normal occlusion with the teeth of the lower jaw, is the treatment of choice. Fixed or removable dental bridgework may be indicated in some patients to secure the desired occlusion and aesthetic result.

In younger patients with a full complement of normal teeth, examination of study casts made from impressions of the upper and lower teeth may reveal that surgical refracturing of the maxilla and repositioning will restore normal occlusion and efficient mastication. The horizontal plane of the surgical refracturing should be just above the level of the floor of the nose. We have used small chisels and osteotomes for the division of the vomer, both antronasal walls of the inferior meati of the nose, and the buccal walls of both maxillary sinuses. The posterior

attachments in the pterygoid region were then separated by prying the jaw loose. The maxilla was then repositioned and immobilized in the manner already described (Figs. 1, 2, 3, 5, and 7).

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SOME OBSERVATIONS ON THE QUICK HIPPURIC ACID TEST IN HEPATIC FUNCTION*

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AT PRESENT it is generally considered that the conjugation of hippuric acid is at least as accurate and reliable as other liver function tests now in general use. Other authors have described in detail the technique,[1] the advantages and disadvantages[1, 2, 6, 7] and the clinical application of this test.[2, 4] It is the purpose of this paper to suggest that a more careful analysis should be made of the patients on whom this test is to be employed, with respect to available carbohydrate for purposes of metabolism, in order that fallacious interpretation of the degree of hepatic function may not be made.

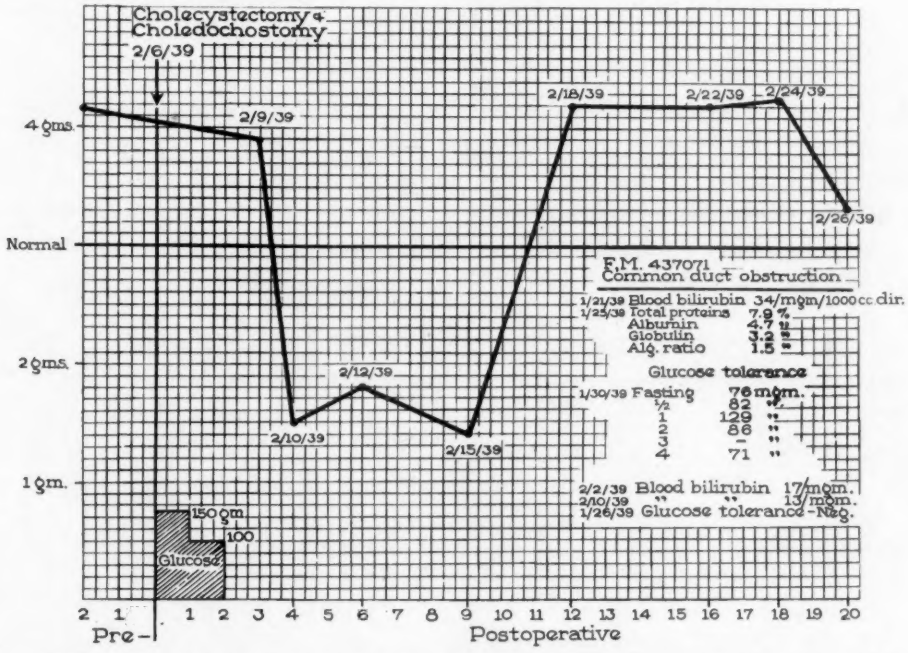

Fig. 1.—This chart demonstrates the immediate postoperative effect of supporting intravenous glucose in sustaining a normal hepatic function. The apparent depression in liver function from the fourth to ninth postoperative days was following the cessation of intravenous glucose and before the patient was able to resume a diet adequate in carbohydrate.

In this study 252 tests were done on 69 patients. In a series of patients not exhibiting clinical or laboratory evidence of liver damage, and in whom no operation was performed, uniformly normal values were obtained, confirming the work done earlier by Quick,[1] Vaccaro,[6] Boyce and McFetridge,[2] and others. In approximately thirty patients with

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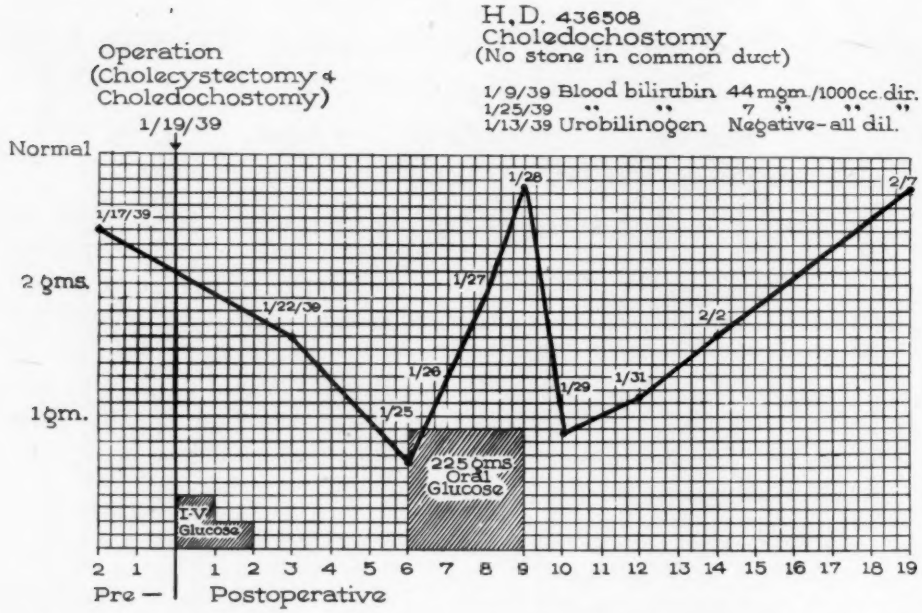

Fig. 2.—This chart demonstrates the apparent depression in hepatic function following cessation of intravenous glucose and the return to normal when large amounts of oral glucose were given. As a normal diet was resumed on the twelfth to fourteenth postoperative days, the excretion of hippuric acid again returned to normal.

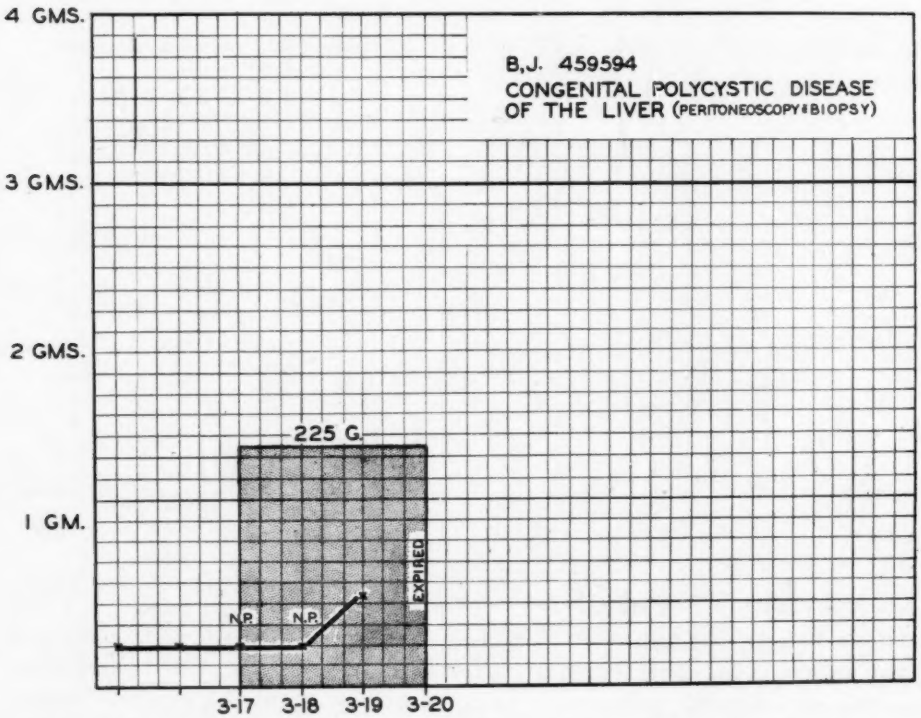

Fig. 3.—In a positively demonstrated case of severe liver damage, large amounts of carbohydrate failed to change significantly the hippuric acid excretion. *N. P.* No precipitate.

and without clinical evidence of biliary disease on whom some type of surgical procedure was carried out, multiple hippuric acid tests were made.

Coleman,[5] using the bromsulfalein test, and Boyce and McFetridge,[2] using the hippuric acid test, have found immediate depression in the liver function following anesthesia, and have assumed that temporary damage to the liver occurred. Boyce and McFetridge have also suggested that this depression is affected by the amount of glucose ingested prior to the test.

In this series, depression of the conjugation of hippuric acid did not occur postoperatively until after cessation of intravenous or oral glucose. At a point in the convalescence of the patient where a normal diet was tolerated (Fig. 1), or where intravenous dextrose was again employed for some untoward complication (Fig. 2), the excretion of hippuric acid again reached a normal level. Conversely, in a few patients where clinical or later autopsy evidence of severe liver damage was present (Fig. 3), no amount of intravenous or oral carbohydrate was sufficient to raise the excretion of hippuric acid to a normal level.

It may be assumed then that a liver with an insufficient amount of carbohydrate does not act as a normal liver, and does not conjugate benzoic acid and glycine in a normal manner or in normal amounts. Another less probable explanation is that in a liver low in carbohydrate, the amino-acid glycine, which ordinarily is present in adequate amounts in the body to conjugate with benzoic acid, must be used to metabolize the fats if acidosis is to be prevented, and thus an insufficient amount is left to give a normal hippuric acid value.

It is suggested then that if the hippuric acid test is to be of value in estimating hepatic function, enough carbohydrate must be furnished the patient over a sufficiently long time to make certain that the ability of the liver to conjugate benzoic acid and glycine is not impaired.

CONCLUSION

The use of the excretion of hippuric acid as a test of hepatic function is more reliable when the patient has had an adequate supply of carbohydrate prior to the test.

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POSTOPERATIVE CHOLORRHEA

Report of a Case, With Profound Peripheral Circulatory Collapse (Shock) Due to Excessive Loss of Fluid and Electrolytes Through A T-Tube

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FOSTER and his associates,[5, 6] and Wangensteen and others have stressed the deleterious effects of prolonged loss of bile through biliary fistulas. Less appreciated are the significance and the possible consequences of cholorrhea, which involves the loss of an abnormally large volume of bile over a short period. Clinically, this syndrome is seen as an infrequent postoperative complication of surgery on the biliary tract. Usually it occurs among patients in whom stone in the common bile duct, or occasionally, carcinomatous involvement of the biliary passages, has been associated with chronic biliary obstruction and conspicuous damage to the liver. The appearance of profuse drainage of characteristically pale, thin bile after operation on such patients has been regarded usually as evidence of hepatic failure, and death preceded by such a condition frequently has been attributed to hepatic insufficiency. It appears likely, however, that under such circumstances death often may be caused by secondary depletion of electrolytes and fluids which accompanies cholorrhea, rather than by hepatic insufficiency alone.

The paucity of references to cholorrhea in the literature is rather surprising. Apparently, the first mention of this condition was made by Sadlier, who in 1916 reported 2 cases in which excessive loss of bile postoperatively was accompanied by circulatory collapse. In the first case removal of stones from the gall bladder and common bile duct was followed postoperatively by drainage of 3,000 to 5,000 c.c. per day of remarkably thin, light-colored bile. Five days after operation profound shock ensued. Rapid improvement followed the parenteral administration of large quantities of solution of sodium chloride, but the condition of shock recurred several times, despite treatment, until the eighteenth postoperative day, when excessive discharge of bile abruptly ceased. In the second patient marked cholorrhea developed two days after surgical removal of numerous stones of the common bile duct, and severe shock occurred on the fourth postoperative day. The patient appeared to be in extremis, with ashen color and cold skin, but rallied

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when sodium chloride was administered parenterally. Excessive drainage of bile subsided after thirteen days. Sadlier could find no report of similar cases in the literature and conducted a survey among surgeons especially interested in the biliary tract concerning their experiences with such a complication; eight reported having encountered the condition on a number of occasions, at times with fatal issue.

Walters and Parham in 1922 pointed out that excessive drainage of bile from patients operated upon for obstructive jaundice was an ominous sign of the development of hepatic insufficiency. Their series comprised 6 cases in which death followed some type of biliary operation and 2 of the 6 patients exhibited conspicuous cholorrhea.

Greene, Walters, and Frederickson in 1930 studied the composition of the bile of 9 patients after operative relief of biliary obstruction from various causes. Three of these patients suffered from marked cholorrhea with output of bile varying in quantity to as much as 3,500 c.c. per day. The bile was notably pale and watery in quality. The concentration and total excretion of bile acids and bilirubin were abnormally and consistently low; whereas, the average content of chloride was somewhat higher than in the 6 other cases comprising the series. Greene and his co-workers suggested that in cholorrhea loss of salt was great enough to be of clinical significance and pointed out that loss of fluids on occasion could be great enough to reduce the output of urine.

In 1932 Melchior described 1 case in which profuse cholorrhea after cholecystectomy led to prostration and death twenty days after the operation. In a second case which he described recovery occurred despite a flow of bile as high as 2,000 c.c. per day. In both instances the liver had appeared to be markedly diseased at operation and the draining bile was very pale in color. The author concluded that the profuse flow in each instance must have been the result of marked damage to the liver.

Bile excreted during a period of cholorrhea contains large amounts of mineral base and the loss of electrolytes by this means may be very large. A patient mentioned by Snell lost 80 Gm. of sodium chloride and 11 liters of fluid through biliary discharge during a three-day period. Snell has observed the volume of bile to be as great as 6,000 c.c. per twenty-four hours. He wrote that the concentration of bilirubin in such bile is very low and that the concentration of bile acids is only about one-tenth of normal; whereas, the concentrations of mineral base and chloride are increased as compared to that of normal bile.

The following case is reported because it illustrates rather clearly some of the clinical and chemical consequences of this unusual condition, and, incidentally, an interesting problem in differential diagnosis.

REPORT OF A CASE

An Irish farmer, aged 60 years, came to the Mayo Clinic on July 7, 1940, because of weakness. He had always been dark skinned. During the preceding five

years fatigue and progressive weakness had developed and he had lost 25 pounds (11 kg.). On two occasions he had had attacks of cramping pain in the upper part of the abdomen, accompanied by nausea, vomiting, and diarrhea, followed by passage of dark urine. On one occasion he had had visible jaundice. Fourteen months before coming to the clinic his condition had been diagnosed as "Addison's disease" elsewhere, and he had spent a year in a sanatorium, where he was treated with rest and the administration of sodium chloride and cortical hormone without subjective improvement. One daughter had had tuberculosis. The family history and personal history otherwise were irrelevant.

Results of examination at the Clinic were essentially negative, except for malnutrition, pigmentation of exposed surfaces, and diffuse melanosis. The patient's blood pressure was 128 systolic and 80 diastolic, expressed in millimeters of mercury. The patient was placed on a low salt, high potassium diet, as described by Cutler and associates, to rule out the possibility of Addison's disease. Both the chemical and clinical findings obtained by this procedure were incompatible with such a diagnosis. A four-hour specimen of urine on the third day of the test contained only 27 mg. per 100 c.c. chloride.

Urinalysis disclosed a specific gravity of 1.017; the reaction was acid. Results of tests for albumin and sugar, and microscopic examination, were negative. Reaction to the flocculation test for syphilis was negative. The content of hemoglobin was 13.6 Gm. per 100 c.c., the erythrocyte count was 3,800,000 and the leucocyte count was 3,400. The value for fasting blood sugar was 103 mg. per 100 c.c. A bromsulfalein test of liver function showed retention of dye, Grade 2. The value for plasma bilirubin was 2.0 mg. per 100 c.c.; the reaction to the van den Bergh procedure was indirect. Results of roentgenograms of the thorax and stomach were negative or normal, as were those of analysis of gastric contents. A cholecystogram disclosed a nonfunctioning gall bladder with stones. It was felt these data effectively ruled out Addison's disease, and cholecystectomy was advised.

Operation was performed Oct. 17, 1940. A grossly diseased gall bladder containing stones was removed, and several stones were taken from the common bile duct which was then closed around a T-tube. Macroscopically the liver appeared to be abnormal; biopsy revealed cirrhosis of Grade 2 on the basis of 1 to 4. A decreasing blood pressure during operation was ameliorated by the transfusion of 500 c.c. of citrated blood.

After the operation the patient failed to regain strength as rapidly as expected. Ten thousand cubic centimeters of dextrose solution and physiologic solution of sodium chloride was administered during the first four days, but thereafter the parenteral administration of fluids was discontinued, since the oral intake of fluids and the volume of urine had rapidly reached satisfactory figures. The patient's appetite was extremely poor and he remained very weak.

On the day of operation 700 c.c. of bile drained from the T-tube. The quantity increased by the fourth postoperative day to 2,200 c.c., and thereafter averaged 1,500 c.c. per day. It was light and watery in quality. The total intake of fluid, output of urine, and volume of bile are shown graphically in Fig. 1. On the morning of the eighth postoperative day the patient was weak, sweating, and unable to eat. The flow of urine was scanty (70 c.c. in sixteen hours) and the urine was concentrated. By noon the patient was prostrated and presented the picture of severe peripheral circulatory collapse with rapid, shallow respiration, weak, thready pulse, marked pallor, faint heart sounds and a blood pressure of 70 mm. of mercury, systolic, and 40 mm. of mercury, diastolic. This episode was not accompanied by nausea, vomiting, diarrhea, hiccough, or abdominal pain. Because of the previous suspicion of Addison's disease, and the fact that the present state bore some similarity to acute adrenal cortical insufficiency, complete studies of blood chemistry were obtained, and without waiting for the results, vigorous treat-

ment by means of the intravenous administration of dextrose solution and solution of sodium chloride and adrenal cortical extract was instituted. Spectacular improvement followed in a few hours.

Forty-eight hours later the patient's condition appeared to be entirely satisfactory, and the intravenous administration of fluids again was discontinued. Recovery continued to be slow, and although circulatory collapse did not occur again, subsequent studies in blood chemistry on the fourteenth postoperative day indicated that such a state was again imminent. The patient once more received fluids intravenously and was given adrenal cortical extract. After administration of these was discontinued three days later, 10 Gm. of sodium chloride and 5 Gm. of sodium citrate were given daily by mouth. Clamping of the T-tube was begun the fourteenth day, and despite some discomfort to the patient, the tube remained closed after the twentieth postoperative day. From the fifteenth postoperative day onward the patient improved steadily, gaining weight and strength. His subsequent convalescence was essentially uneventful.

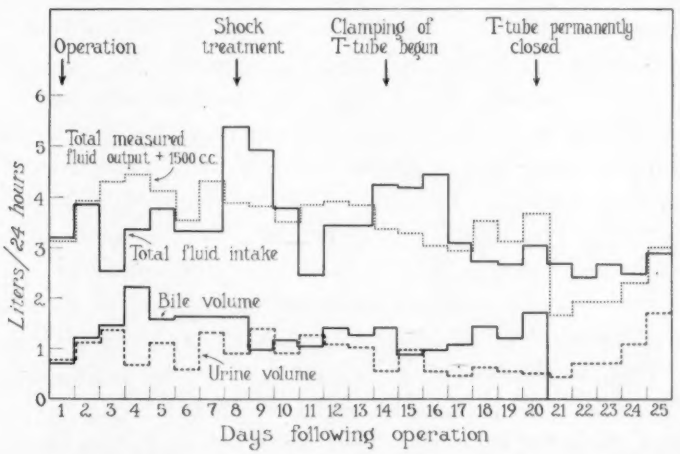

Fig. 1.—Fluid intake and output. To the measured fluid output has been added 1,500 c.c. per day to account for insensible fluid loss. The total output as estimated in this manner exceeded the intake during part of the first week postoperatively, although not by impressive amounts.

COMMENT

When first examined at the Clinic, this patient presented an interesting diagnostic problem. Addison's disease had been diagnosed elsewhere for him, for obvious reasons; marked asthenia, malnutrition, and pigmentation were present. However, pigmentation was limited to brown discoloration of exposed parts and a diffuse bronzing of the trunk. The creases of the palms, body folds, scars, and mucous membranes were not pigmented nor were black freckles, characteristic of adrenal disease, apparent. Adequate adrenal function was indicated by results of the salt deprivation test, and the demonstration of hepatic disease associated with cholelithiasis was felt to afford a perfectly adequate alternative explanation of all the symptoms.

When seen on the eighth postoperative day, the patient presented a picture of severe prostration and extreme peripheral circulatory collapse which again might have been mistaken for the crisis of Addison's

disease. There were a number of reasons for the belief, however, that his condition did not represent adrenal cortical insufficiency: (1) results of the salt deprivation procedure done two months earlier had been entirely satisfactory and completely negative; (2) the clinical picture differed from that of acute adrenal cortical insufficiency in the absence of vomiting, diarrhea, hiccoughs, or abdominal pain; (3) the patient had survived a long and difficult operation and six days of convalescence, a course of events most improbable for a patient suffering from untreated Addison's disease; and (4) results of chemical studies of the blood and urine differed from those encountered in Addison's disease.

Because of the previous uncertainty as to the correct diagnosis, the patient was subjected to rather intensive study during the ensuing two weeks. Samples of blood were collected under oil and centrifuged. After the hematocrit value had been determined, the plasma was removed and examined for specific gravity, and for content of sodium, potassium, chloride, total protein, nonprotein nitrogen, and urea. Twenty-four-hour samples of urine and bile were analyzed for sodium, potassium, and chloride. Determinations of the specific gravity of the plasma were made by means of the Kagan proteinometer; total protein was determined by means of a modified Kjeldahl method. Details of other chemical analytic methods employed are described elsewhere.[18]

Results of Laboratory Studies.—The laboratory data are summarized in Table I and the changes observed in the blood are represented graphically in Fig. 2. The hematocrit value, specific gravity of the plasma and plasma proteins were employed as indices of hemoconcentration. When the patient was first observed to be in circulatory collapse, all three were proportionately and markedly elevated. The cell volume as determined by the hematocrit was 62 per cent; plasma proteins were 11.0 Gm. per 100 c.c. and specific gravity of the plasma was 1.036. These values suggest a rather marked reduction in plasma volume. In a sample of blood obtained sixteen hours later these determinations were relatively normal, but six days later the figures again indicated increasing hemoconcentration despite the fact that clinical evidence of shock had not developed: the hematocrit value was 52 per cent, specific gravity of the plasma was 1.032, and plasma proteins were 9.5 Gm. per 100 c.c. With additional treatment the indices of hemoconcentration decreased and thereafter remained within normal ranges.

The first specimen of blood analyzed contained 96 mg. per 100 c.c. nonprotein nitrogen, of which 76 mg. per 100 c.c. represented urea nitrogen. That this retention of nitrogen was associated with circulatory collapse and hemoconcentration rather than any intrinsic type of renal insufficiency is shown by the rapidity with which a decrease to normal values occurred. An increase in nitrogen did not accompany the hemoconcentration which took place the thirteenth and fourteenth days

TABLE I

SUMMARY OF LABORATORY DATA

DAYS AFTER OPERATION	PLASMA								BILE				URINE				
	HEMATOCRIT VALUE (% CELLS)	SPECIFIC GRAVITY	TOTAL PROTEIN, MG. PER 100 C.C.	CHLORIDE, MEQ./L.	SODIUM, MEQ./L.	POTASSIUM, MEQ./L.	N. P. N., MG. PER 100 C.C.	UREA N, MG. PER 100 C.C.	VOLUME, C.C.	CHLORIDE, MG. PER 100 C.C.	SODIUM, MG. PER 100 C.C.	POTASSIUM, MG. PER 100 C.C.	VOLUME, C.C.	SPECIFIC GRAVITY	CHLORIDE, MG. PER 100 C.C.	SODIUM, MG. PER 100 C.C.	POTASSIUM, MG. PER 100 C.C.
1									700				750				
2									1205				1100				
3									1440				1350				
4									2160				700				
5									1520				1125				
6									1535				550				
7									1540				1265				
8	61.3	1.0355	11.0	76	128	4.3	98	76	1540				880				
9	44.8	1.0265	7.2	90	127	3.5	61	56	960				1340	1.022	2291	710	796
10	45.6	1.0270	7.4	89	127	4.0	39	32	1145				860	1.022	464	77	194
11									1050				1250				
12									1315				1075				
13	48.2	1.0300	8.7	84	120	5.2	43	39	1250				1600				
14	52.7	1.0313	8.7	81	121			35	1320	5491	4224	277	520	1.021	166	62	249
15	49.0	1.0279	8.0	91	125	5.1	44	31	825				950				
16	43.1	1.0256	7.0	95	130	5.2	32	23	985				525				
17									1075				400	1.019	1120	532	426
18									1400				645	1.021	3502	2477	481
19									1150				540	1.022	3105	2257	380
20	33.9	1.0253	6.9	98	136		25	16	1700	7786	5479	373	500	1.021	3615	3000	359
21													400		2852	2496	464
22	39.1	1.0243	6.4	99	133	5.3	22	16					700	1.018	5474	4515	758
23													700				
24													1065	1.021	9191	6880	1105
25													1770	1.014	8284	5894	885

after operation, indicating that impairment of circulation of a degree sufficient to affect renal function had not occurred on the second occasion.

Study of the plasma electrolytes revealed equally profound alterations. The first sample of blood contained 76.4 meq. per liter of chloride; whereas, the plasma sodium was reduced proportionately only about one-half as much as the chloride (128.2 meq. per liter). The figure for plasma potassium, 16.9 mg. per 100 c.c., is at the lower limit of normal and is of interest chiefly because it indicates, contrary to the inference of Scudder and others, that the classic picture of shock and hemoconcentration may occur without associated hyperpotassemia.

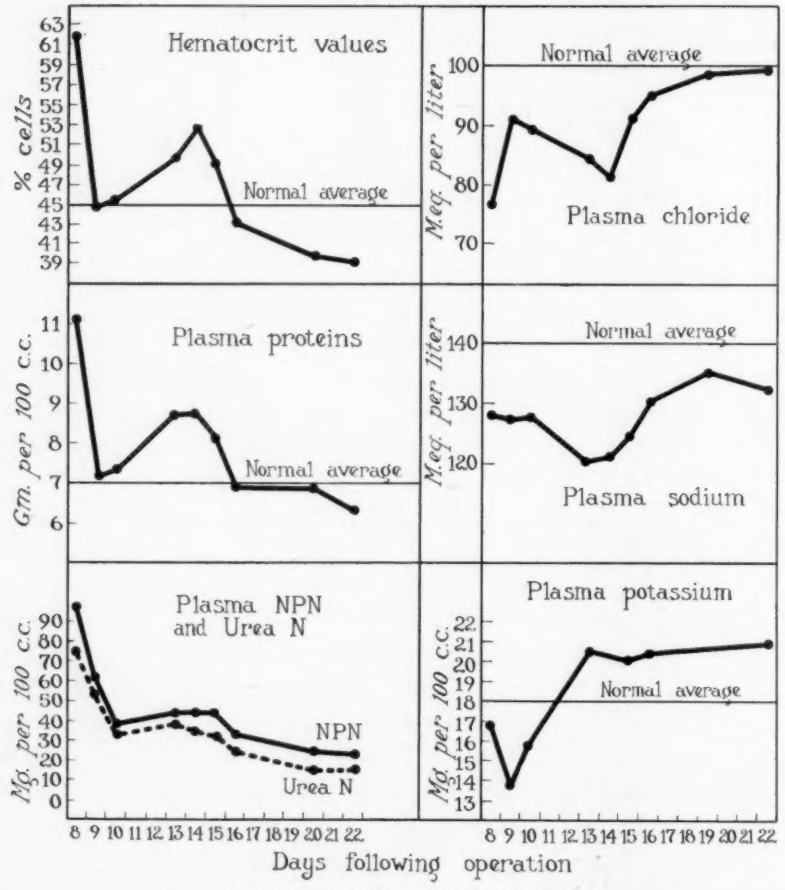

Fig. 2.—Determinations of blood chemistry.

The figures we have just presented for plasma electrolytes are not entirely typical of the crisis of adrenal cortical insufficiency, in which a high content of plasma potassium and a low content of plasma chloride and sodium usually are to be found, but with sodium depleted to a greater extent than chloride. Furthermore, the extremely small quantities of sodium and chloride in the urine on days on which extra salt was not administered does not suggest adrenal cortical insufficiency.

That the kidney could adequately conserve electrolytes is shown by the fact that on such days the urinary concentration of these substances was extremely low: for chloride, 32 to 54 mg. per 100 c.c. and for sodium 8 to 12 mg. per 100 c.c. The parenteral administration of solution of sodium chloride, on the other hand, was accompanied by the usual marked increase in the excretion of both salt and water in the urine, so that an appreciable proportion of the salt thus administered probably was soon lost.

The daily output of bile was uniformly large: 1,500 to 2,000 c.c. per day during the first week, and 1,000 to 1,700 c.c. thereafter (Fig. 1). The samples of bile analyzed contained extremely high concentrations of chloride (117 to 129 meq. per liter) and were proportionately high in sodium; values for both ions far exceeded contemporary values for the same ions in the plasma (Table II). The concentration of potassium in the bile, however, was little if any higher than in the plasma. The significance of these observations is shown by the fact that on a day on which 2,000 c.c. of bile was excreted, 17 Gm. of sodium chloride was lost by this route alone.

TABLE II

COMPARISON OF ELECTROLYTE CONCENTRATION IN PLASMA, BILE, AND URINE*

DAY AFTER OPERATION	CHLORIDE			SODIUM			POTASSIUM		
	PLASMA	BILE	URINE	PLASMA	BILE	URINE	PLASMA	BILE	URINE
	MILLIEQUIVALENTS PER LITER								
14	81	117	9	121	140	5	4.3	5.4	11.6
20	99	129	210	137	146	262	5.2	5.6	18.4

*First day noted (fourteenth) is one on which no extra salt was administered, and a state of relative depletion of salt existed. Second day noted (twentieth) is one on which an excess of salt existed.

Comparatively little information is available concerning the electrolyte content of apparently normal bile which is drained externally. The recent monograph by Sobotka summarized most of the published data on this subject. Tschopp (cited by Sobotka) found in normal fistula bile 96 meq. of chloride and 4.9 meq. of potassium per liter. Greene and his co-workers found that bile excreted by their patients contained a concentration of chloride varying from about 90 to 130 meq., but averaging about 110 meq. per liter, figures in many instances above normal plasma levels. Accurate data for the sodium content of normal human bile are not available, but Rheinhold and Wilson found that apparently normal bile drained from an external fistula in dogs contained an average of 174 meq. of sodium as compared to values for sodium in the plasma of 148 meq. per liter in the same animals.

Fluid and Salt Balance.—The figures for intake of fluids as compared to those for the total output of fluids appeared to be satisfactory on the patient's chart. If, however, an increment of 1,500 c.c. per day is added to the measured output to account for insensible loss of water, as suggested by Coller and Maddock,[2, 3] the loss of fluids during the

first week is shown to have exceeded the intake, although not by impressive amounts (Fig. 1). Except for the solution of sodium chloride administered intravenously the first few days postoperatively, the intake contained very little salt, for the patient ate little and the fluids taken by mouth, although they were of fairly satisfactory volume, were virtually salt-free. By contrast, the fluid excreted, especially the bile, contained large amounts of salt. On this basis the resultant hypochloremia and circulatory collapse may be explained.

An estimate of the probable daily salt balance has been made for the entire postoperative period. These balances are shown graphically in Fig. 3. From the diet record was calculated the maximal possible intake of chloride, and for days on which no laboratory data were available, a minimal output of chloride in the urine was postulated. The average

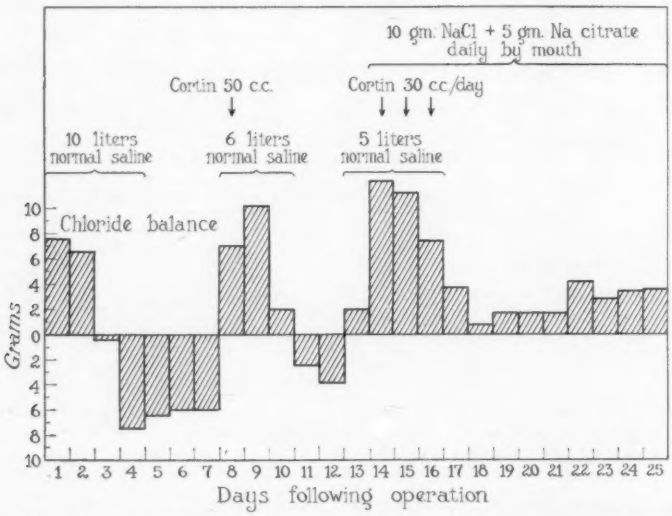

Fig. 3.—Estimated chloride balance. The difference between the estimated intake and estimated output of chloride ion is shown as "grams retained" or "grams lost" per day. Marked chloride depletion preceded the appearance of shock on the eighth postoperative day.

values for chloride were applied to all bile excreted. The differences between the values for intake and output of chloride were assumed to represent a conservative measure of the loss of salt when such loss occurred. It may be seen from the graph that the time of circulatory collapse is preceded by several days, during which the excretion of chloride exceeded the intake by large amounts, and that a similar negative balance was inadvertently allowed to occur during several days preceding the second period of hemoconcentration. By the time the latter had occurred, the underlying disturbance was recognized; extra salt and extra sodium were administered regularly thereafter, partial closure of the T-tube was expedited and subsequent recovery was without further incident. There is no reason to believe that the adrenal cortical extract administered as emergency treatment in this case played any significant role in the patient's recovery.

The physiologic basis for cholorrhea is entirely unknown. The present case and the others in the literature amply document the statement that cholorrhea apparently is a manifestation of serious hepatic damage. Presumably, the damaged liver loses the capacity to excrete bilirubin and to form bile salts while it retains the ability to excrete chloride and base in concentrations which are higher than those present in the blood. Brand has stated that bile shows a remarkable tendency to maintain a constant osmotic pressure which is equal to that of the plasma and that variations in one of the constituents of bile are compensated for by sufficient alteration of others to maintain the normal osmotic pressure. On this basis one of the fundamental disturbances in cholorrhea is a decreased ability of the hepatic parenchyma to excrete bile acids. Under such circumstances the chloride content of the bile is necessarily greater than that of normal hepatic bile.[10]

SUMMARY

The syndrome of postoperative cholorrhea occurs occasionally as a complication of surgery of the biliary tract. It is perhaps most frequently encountered among patients who have hepatic disease associated with stones in the common bile duct, but also may be encountered in the presence of chronic biliary obstruction from other causes. It is characterized by profuse drainage of pale, thin bile containing markedly decreased quantities of bilirubin and bile salts and excessive concentrations of chloride and mineral base. The cases heretofore reported lead the investigator to believe that the presence of this condition is a serious prognostic sign. Loss of fluids and of large quantities of electrolytes by means of such excessive biliary drainage may lead to dehydration, hypochloremia, and circulatory collapse. It seems probable that deaths may have occurred from these secondary factors rather than from hepatic deficiency.

A case is presented in which cholecystitis and stones in the common bile duct associated with cirrhosis of the liver and evidence of impaired hepatic function produced certain clinical and chemical features bearing a superficial resemblance to Addison's disease. Postoperative cholorrhea, its implications at first unrecognized, led to profound electrolyte depletion, hypochloremia, hemoconcentration, and circulatory collapse. Adequate and persistent replacement of salt and mechanical termination of the external flow of bile were followed by completely satisfactory convalescence.

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HEMANGIOMA OF THE LIVER

Discussion of Symptomatology and Report of Patient Treated by Operation

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ALTHOUGH small hemangiomas of the liver are not uncommonly seen incidentally at post-mortem examination,* such tumors rarely grow sufficiently large to cause symptoms or signs which lead to operative treatment. Because of this fact, and possibly also because some surgeons when confronted with the problem of dealing with a blood vessel tumor in a notoriously vascular organ may have refrained from resection for fear of uncontrollable hemorrhage, the number of reported cases in which resection has been carried out is not large, and no author has published a report of more than a single case.

When I recently came upon a large hepatic hemangioma during a laparotomy, the puzzling question presented itself whether the tumor was causing the symptoms of which the patient complained and whether resection would relieve her of her distress. Like certain other lesions which are ordinarily small and asymptomatic and rarely are large enough to produce complaints, the symptoms which may be attributed to hemangioma of the liver are not commonly known, the criteria upon which a preoperative diagnosis may be postulated are not fully understood, and the efficacy of treatment is not definitely appreciated. I have consequently felt it advisable to report this case and to analyze the case records in the literature in regard to the clinical picture which these tumors present and the outcome of operative treatment. I shall deal only briefly with the technique of resection. From time to time certain fundamental contributions to the operative removal of liver tumors in general and of hemangiomas in particular have been made, and the problem has been discussed in several recent papers.[73, 75] I shall not include in this study malignant hemangioendotheliomas.[5, 37]

CASE REPORT

C. E., a colored married female, 40 years of age, was admitted to the Johns Hopkins Hospital on April 21, 1940, complaining of epigastric discomfort. She stated that her present illness had begun at least fifteen years before and had continued except for occasional remissions which did not last more than a few weeks, and that during this time she had had nearly constant gnawing discomfort in the upper abdomen. The trouble had become steadily worse and had been especially bad in recent months. She complained of a continual feeling of fullness and of a constant "sour feeling" with occasional eructation but with little or no vomiting.

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*Hemangiomas occur more often in the liver than in any other internal organ.[24] In the majority of instances these are solitary tumors.

Sometimes there was a "quivering" sensation in the upper abdomen and sometimes, she said, the gnawing discomfort was somewhat as if she could feel her heart beating in the epigastric region. She said that soda, milk, and food brought some temporary relief, but rarely for longer than an hour or an hour and a half at most. The discomfort was especially annoying at night, often waking her from a sound sleep. She had never had hematemesis or melena. She said that her weight had fluctuated greatly during the past twenty years and that she had recently lost weight.

Examination of her voluminous dispensary record showed that she had been a frequent visitor to the gastrointestinal clinic since 1927, when she first came because of upper abdominal discomfort and constipation of seven years' duration. The complaints were repeatedly the same: "gas," "misery," "gnawing" or "quivering" sensation in the "pit of the stomach." During the fourteen years of observation she had been treated with various alkalies, diet, mineral oil, belladonna, bromide, and hyoscyamus compound. There were fluctuations in her distress but rarely relief for any length of time. She had had numerous gastric analyses. The fasting free acid varied from 14 to 42, the total from 39 to 78. In 1931, after the administration of histamine, the free acid was 66, the total 76. From time to time gastrointestinal fluoroscopy was done. In 1927 the stomach was said to be atonic but

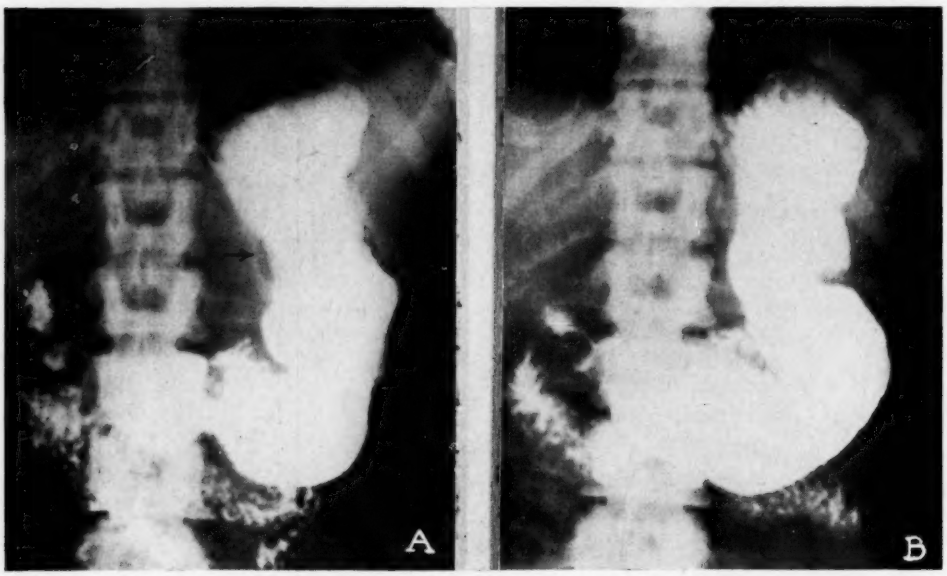

Fig. 1.—Gastrointestinal x-rays. *A*. Before operation, April, 1940. The pressure defect on the lesser curvature from an extrinsic mass and the deformity of the duodenal bulb were constant in all films. *B*. After operation, May, 1940. The pressure from the extrinsic mass is no longer present. Deformity of the duodenal bulb persists.

without intrinsic lesion. In 1937 the stomach and duodenum were described as normal. In March, 1939, the pylorus was said to be spastic. X-rays taken in October, 1939, showed a pressure defect of the lesser curvature from an extrinsic mass and deformity of the duodenal bulb thought to be due to an old ulcer. Two subsequent gastrointestinal series presented essentially the same picture (Fig. 1 *A*). Cholecystograms in 1939 showed no pathologic changes. A number of stool examinations were negative for occult blood. During the period of observation her hemoglobin varied between 60 and 70 per cent. A complete blood examination in April, 1940, was as follows: erythrocytes, 4.47 millions; hemoglobin 8.5 Gm. (60 per cent); hematocrit, 32; mean corpuscular volume, 72 c. microns; mean corpuscular hemoglobin, 19 micromicrograms; mean corpuscular hemoglobin concentration, 27 per cent; sedimentation rate, 7 (corr.); icterus index, 4. The impression had varied,

ulcer being suspected from time to time. When this diagnosis was thought to have been established, she was admitted to the hospital for operation.

The patient had had many other complaints. Since 1926 she had been under treatment or observation for syphilis. She had been treated off and on in the nose and throat clinic since 1927 for bilateral maxillary sinusitis, and since 1933 she had been under treatment in the protein clinic for asthma. She had been thought by some to have infectious arthritis, but in 1940 the physicians in the arthritic clinic had failed to find any evidence of arthritis and thought her joint complaints were entirely subjective. She had been seen in the gynecologic clinic on numerous occasions and had been treated for chronic salpingitis, trichomonas infection, and ureteral stricture. It seemed to be generally felt that in addition to many organic complaints she had a definite tendency to hypochondriasis. Her family history was noncontributory.

On admission the temperature was 99.4° F.; the pulse, 96; the respirations, 22; and the blood pressure, 146/90. On general examination nothing abnormal was found except a small ill-defined mass just below the xiphoid which descended with respiration and was slightly tender to palpation. It could not be outlined sufficiently well to permit an accurate opinion as to its size, contour, or consistency. The Wassermann reaction was negative, the urine essentially normal, the hemoglobin 54 per cent. The day after admission the patient was given a transfusion of 500 c.c. of citrated blood, which raised the hemoglobin to 63 per cent.

It was thought that the patient had a chronic duodenal ulcer. The presence of the mass raised the question whether she might have a gastric carcinoma with metastases to the liver.

Operation.—Exploratory laparotomy, excision of hemangioma of liver, April 23, 1940. Under ether anesthesia a high left paramedian incision was made, the peritoneum was opened, and the viscera were inspected. In the first portion of the duodenum was a small diverticulum, smaller than the distal phalanx of one's little finger. No ulcer was seen and the pylorus was patent and not scarred. Some observers thought there was evidence of very slight scarring on the anterior surface of the duodenum just beyond the pylorus, but this was not definite and there was no conclusive evidence that the patient had ever had a peptic ulcer. The stomach was entirely normal, as were the gall bladder and the intestinal tract. Attention was immediately attracted to a large cavernous hemangioma about the size of a man's fist, which occupied most of the left lobe and which pressed upon the upper portion of the lesser curvature of the stomach (Fig. 2). It was felt that this lesion most likely accounted for the patient's symptoms. The ligamentous attachment of the left lobe of the liver to the diaphragm was divided, permitting adequate mobilization of the lobe. Large Kelly clamps were placed across the liver about 1.5 cm. beyond the margins of the tumor, and the tumor was quickly excised by sharp dissection. The clamps held along the margin of the liver where the liver was thin, but cut through deeper in where the liver was thick. The pedicle of the lobe was being compressed between two fingers, however, and there was surprisingly little bleeding. Through-and-through mattress sutures of medium silk were placed just within the clamps and the clamps were removed. Release of pressure on the hilar structures demonstrated a number of bleeding points; these were clamped with hemostats and coagulated with the electrocautery. The mattress sutures had approximated the serosal edges of the liver in its thin peripheral portion, but it was impossible to accomplish this centrally because of the thickness of the liver. The bed was now dry. A cigarette drain was so placed that the end of the gauze was in contact with the denuded liver surface. The wound was closed in layers with interrupted silk sutures. The patient stood the procedure well.

Pathologic study showed the excised tumor to be a typical cavernous hemangioma, made up essentially of large sinuses filled with blood and lined by typical endothelial cells. The interstices were made up of moderately dense connective tissue.

The normal liver surrounding the tumor showed no scarring but some mononuclear inflammatory infiltration in the portal spaces (Fig. 3).

The postoperative course was uneventful. The patient was comfortable. For five days there was a slight elevation of temperature which only once exceeded 100° F. For a few days there was light serohemorrhagic drainage but no biliary drainage. The drain was gradually shortened and was removed on the seventh day. She was discharged on the sixteenth postoperative day, the wound being entirely healed. A bromsulfalein liver function test the preceding day showed less than 5 per cent retention.

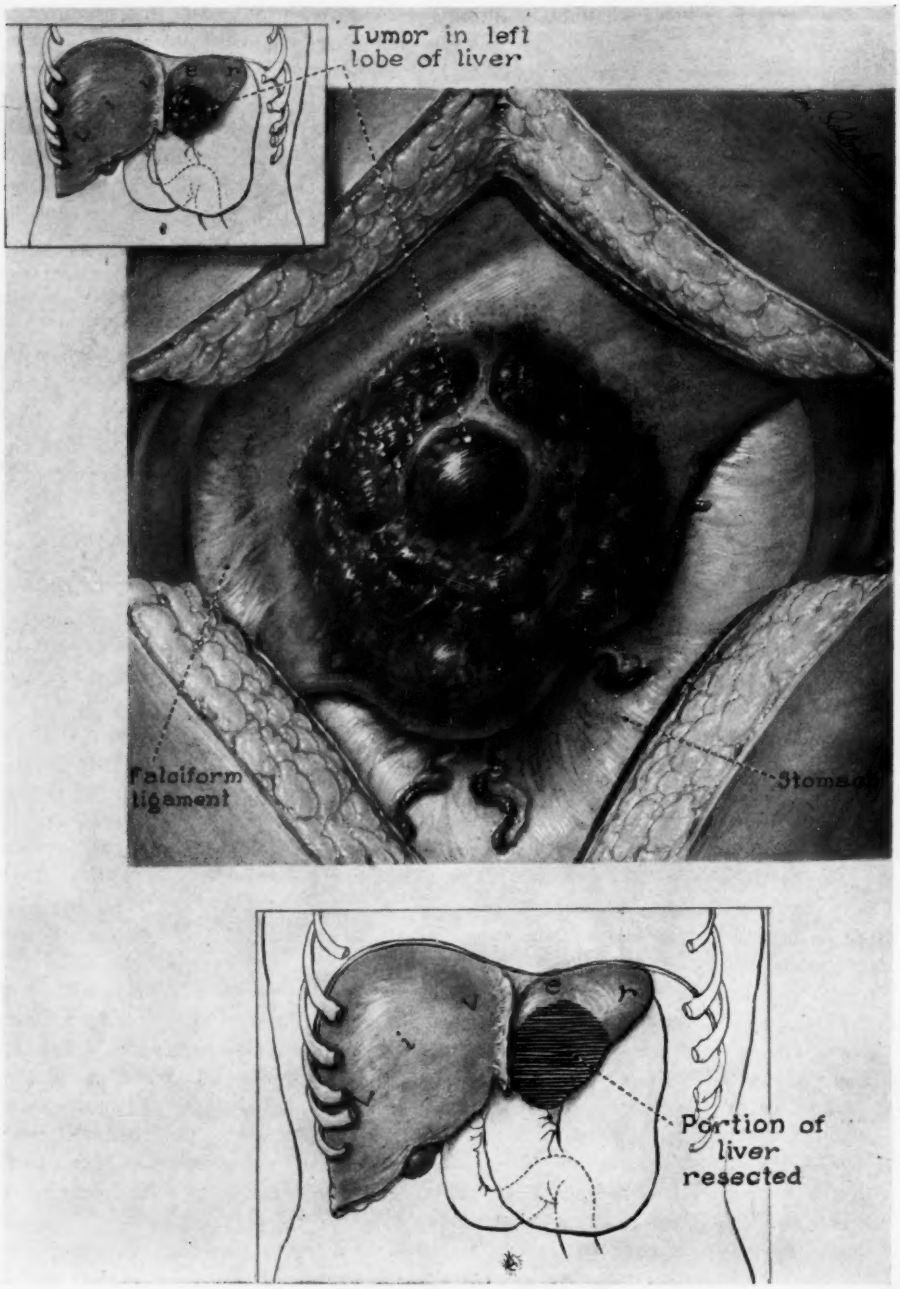

Fig. 2.—Drawing of the tumor made at operation.

When the patient first left the hospital, she complained of a sense of fullness and occasionally of slight regurgitation upon eating a large meal, but this difficulty soon ceased on a regimen of six small daily feedings which she followed for a few weeks. After this she was able to take a normal diet without difficulty. Gastrointestinal x-rays one month after operation showed normal stomach motility and the same deformity of the duodenal bulb which had been noted before operation (Fig. 1 *B*).

Fig. 3.—Photomicrograph of peripheral portion of the tumor showing large endothelial-lined sinuses and the adjoining liver tissue.

One year after operation she looked well. She had gained in weight and examination was essentially negative except for a keloidal change in the abdominal scar. The liver was not palpable. There was no abdominal tenderness. She stated that she was definitely better than before the operation but was not entirely relieved of her trouble. For ten months she had had good appetite and digestion; bowels had moved regularly with the use of mineral oil; the sense of fullness, the frequent eructation, and the annoying pains which she had had before operation were almost entirely absent. Ordinarily she was not aware of her "stomach"; she complained much more of pains in her joints and in her eyes; and she volunteered that she felt quite well as long as she could keep her mind diverted and did not think too much about herself. During the past two months, however, there had been a return in a mild form of some of her old complaints. She had frequently had a "sick feeling" in her epigastrium which she found difficult to describe and at times a great deal of eructation. These symptoms could be relieved with food, milk, or even water. The gnawing pains had not returned, nor had the "quivering sensa-

tions'' which she said constituted the most distressing complaint before operation. It is apparent that she has by no means obtained complete relief and it remains to be seen whether her symptoms will diminish or increase with the passage of time.*

DISCUSSION

I have found in the literature 66 cases of benign hemangioma of the liver in which operation has been performed.† My case brings the total to 67. In 56 of these the tumor was resected.

The youngest patient in this series was 6 years old,[54] the oldest 76;[7] and the average age was 44 years. Operation was most commonly performed in the third and fourth decades (58 per cent). Seventy-five per cent were between 30 and 60 years old at the time of operation.

Females were affected in a ratio of about 4.5 to 1 male. Fifty-one of 62 patients on whom data are available were females.

In about one-half of the cases the initial complaint was of a tumor mass in the epigastrium or some equivalent symptom such as increase in the size of the abdomen, and about one-half of the patients first complained of pain or some digestive disturbance. Twenty-eight of 61 patients on whom data are available had first some such complaint as a tumor or abdominal swelling, and at least 21 of them were aware of a definite tumor mass. In addition, 4 patients had their attention called to the presence of a tumor by their physician; 2 of these never developed any symptoms. In 12 other instances in which the illness began with pain or some other symptom the patient subsequently complained of a tumor or of abdominal swelling.

The 32 patients whose initial difficulty was a tumor or abdominal enlargement had noticed this for a period of time varying from a few months to over 30 years, and on an average this complaint dated back about 5½ years. Apparently in 6 of these patients no other symptoms appeared. One complained of nothing except weakness and evening fever, 2 of slight local discomfort, 7 of a sense of weight or pressure. One had dysmenorrhea, 1 dysuria, 2 pain in the back or legs. Twelve of them complained of severe or mild epigastric pain or of a sense of heaviness, pressure, or fullness in the upper abdomen, often associated with other symptoms such as eructation, nausea, or vomiting. In some instances the distress was largely postprandial.

Not only was pain or digestive difficulty the commonest of the symptoms which subsequently appeared in the group of patients whose illness first became manifest by an abdominal tumor or enlargement, but ''dyspepsia,'' ''stomach trouble,'' abdominal pain or discomfort usually epigastric, nausea, vomiting, anorexia, and other gastrointestinal complaints

*At the time of publication the patient is considerably better. She has had very little difficulty in recent months, has not required soda or other medicine, and has continued to gain weight. She says that her health has been decidedly better during the year and a half since operation than any time during the past fifteen or twenty years.

†A few papers which may contain a few additional cases are not available to me. In discussing Tinker's paper[72] E. Beer mentions a case of hemangioma of the liver in which he had difficulty in controlling the bleeding. No other details are given and the outcome is not stated.

initiated the illness in nearly one-half of all the patients. This was the case in 27 patients. In 3, in all of whom there had been spontaneous rupture of the hemangioma, the illness was of short duration and suggested acute appendicitis, ruptured tubal pregnancy, or peritonitis.[15, 43, 72] In most, however, the complaints were of a chronic nature, beginning in some instances as long ago as ten or twenty years before operation. The average duration of symptoms was nearly five years. In 17 patients the complaints were largely referable to the stomach. Some are said to have had "stomach trouble" or "indigestion"; in most there was definite epigastric distress or pain, frequently postprandial. An occasional patient localized his discomfort in the right or left upper quadrant, but more commonly it was in the midepigastrium. Sometimes the discomfort was described as of an unusual nature such as "whirring," "tearing," or "dragging." Nausea, vomiting, and anorexia were not uncommon. One patient had definite melena and hematemasis.[46] A few had difficulty in swallowing. In general, the symptoms at the beginning of the illness were commonly such as to direct attention to the stomach, although subsequently the belief was often held that there was some extragastric lesion because all of these patients had a palpable tumor at the time of operation. In 7 patients, on the other hand, the symptoms rather suggested gall bladder or biliary tract disease; in 3 of these the symptoms were apparently due to the hemangioma as resection of the tumor brought about relief of symptoms. Interestingly enough, in a fourth[70] the hemangioma caused a hydrops of the gall bladder by pressure on the neck of the gall bladder, and excision without further operative procedures effected a cure. In 3 instances there was associated gall bladder disease and hemangioma of the liver. In 1 patient[59] the gall bladder appeared normal and the hemangioma alone was resected; the complaints, however, continued until a cholecystectomy was subsequently done. The pathologic report was chronic cholecystitis. In another[27] the hemangioma was resected at the same time the cholecystectomy was done. In the third[30] the hemangioma was discovered only at autopsy, having been overlooked in three successive operations for cholelithiasis.

One patient complained of headache, vertigo, anorexia, and fatigability; another,[31] a patient who had suffered a spontaneous rupture of a hemangioma, complained only of weakness; in a few cases the history is not given.

In only a few cases is it definitely stated that a tumor was not palpable, and in 54 a tumor was easily felt. In general, nothing characteristic was noted about the tumor mass. In 1 instance a murmur on auscultation and a history of a whirring or buzzing sensation led to the correct diagnosis before operation.[4] Another tumor was so compressible as to lead the examiner to suggest the correct diagnosis.[29] Ordinarily, however, nothing unusual was noted on palpation of the mass. Unfortunately, in almost all the cases, as in my own, ausculta-

tion was not carried out. The tumor was most commonly palpated in the left upper quadrant of the abdomen or just below the xiphoid. It was found to arise from the left lobe in 30 cases, from the right in 18, from the spigelian in 1, in an accessory lobe in 1, in a "*Schnurrlappen*" in 1. In 5 instances the origin was apparently from multiple lobes; 1 tumor arose from both right and left lobes, 2 from the left and quadrate lobes, 1 from the left, quadrate, and spigelian lobes, and 1 from the right and quadrate lobes. The size of the tumor was variously described; it was said to be the size of a prune, hazelnut, walnut, goose egg, gall bladder, apple, orange, man's fist, fetal head, child's head, man's head, pregnant uterus. In 17 instances where actual weights are given the tumor, generally in the collapsed state, weighed from 58 to 2,500 Gm. and averaged about 900 Gm. In 18 instances in which measurements are given the size varied from 9 by 5 cm. to 32 by 22 by 9 cm. and averaged about 12 by 12 cm. In 23 cases the tumor was more or less pedunculated; in 8 of these the pedicle was large and broad.

In 12 cases gastrointestinal x-rays were taken. In 1 case,[76] in which the patient had had gradually increasing difficulty in swallowing foods until finally no solids could be taken, x-rays showed considerable retention of barium in the lower portion of the esophagus, and the patient was operated upon with a preoperative diagnosis of carcinoma of the cardia. In 8 cases the stomach was seen to be pushed over to the left or downward or to have an extrinsic mass pressing upon the lesser curvature, often lengthening the lesser curvature.[2, 18, 23, 58, 65, 67, 68] In 1 case[48] the colon was displaced by a mass in the right upper quadrant. In 2 cases gastrointestinal series were said to have showed nothing abnormal.[27, 69] In 8 of the 11 cases in the literature the x-rays were rather similar to those in my case.

The correct diagnosis was made only twice before operation.[4, 29] In 4 other instances it was suggested as a possibility along with others. In a few cases the preoperative diagnosis is not given; in others numerous possibilities are listed. Tumor of the liver was suggested 13 times, hepatic echinococcus cyst twice, "liver disease" twice, tumor or cyst of the pancreas 9 times, mesenteric tumor or cyst 5 times, omental tumor 4 times, and adrenal tumor once. Renal tumor was considered twice, mobile kidney 4 times, tumor of the gall bladder 3 times, hydrops 3 times, cholecystitis twice, cholelithiasis once. Ovarian tumor or cyst was considered in 7 cases, uterine myoma in 1. Carcinoma of the stomach was suspected in 2 cases, peptic ulcer in 1. Other diagnoses were acute appendicitis, abdominal abscess, peritonitis, intestinal tumor.

In 56 instances resection was carried out. Only 1 of these patients died. This patient had a tumor in the right lobe lateral to the gall bladder in the periphery of the liver without pedicle. During the operation there was shock although comparatively little blood was lost, and the patient died in eighteen hours.[41] In all other instances resection was attended by recovery. Various procedures were employed. In 23 cases

the tumor was pedunculated, in 8 of which the pedicle was very large. The problem in these cases, even when the pedicle was very broad and thick, was greatly simplified. When small, the pedicle was simply ligated with a transfixing ligature and divided. With the larger pedicles several hemostatic sutures were necessary. Sometimes a V-incision was made through the pedicle to permit approximation of the serosal surfaces. In one of the early cases Rosenthal,[62] finding a sort of pedicle, placed an elastic tourniquet about it, extra-abdominalized the mass with a needle through the pedicle, cut through the pedicle with the cautery, and packed with iodoform gauze. In another early case, Keen,[32] confronted with a large tumor in the left lobe, cut into the liver on both sides, thus making an artificial pedicle. Elastic rubber tubes were secured about its base as a tourniquet, iodoform gauze was packed below the tourniquet, and the tumor, tourniquet, and gauze were brought out through the wound. The tourniquet was removed some days later, the tumor excised, and the defect closed with skin grafts. In another early case Pfannenstiel[38] also made an artificial pedicle in a similar manner. He excised the tumor and sutured the cut surface of the liver to the abdominal wall, thus extraperitonealizing it. Beck[3] used rubber catheters over iodoform gauze as a tourniquet, extra-abdominalized the mass with hat pins through the pedicle, and removed the tumor. Israel[29] also used a rubber tube tourniquet and silk ligature, bringing the tourniquet out through the wound. In the first reported case of resection Eiselsberg[19] utilized the cautery and pack. Another early case in which the cautery and pack were used is that of Beck.[4] Smoley[55] used elastic bands as a tourniquet, mass ligatures, and the cautery. He then sutured the liver and employed no drainage. In the more recent cases such devices have not ordinarily been necessary. The cautery has a definite place in controlling bleeding. In Eiselsberg's original case[19] the operator first cut very close to the tumor mass and there was considerable bleeding. When incision was made further out in the normal liver substance, there was much less bleeding. This principle of never cutting through the tumor itself but through normal liver tissue was re-emphasized by Horsley.[27] Eckles[18] found the use of rubber-shod clamps across the liver substance of considerable help. Similarly, placing Kelly clamps across the liver, as was done in my case, may be helpful. V-incisions into the liver substance or into a large pedicle often permit approximation of the serosal surfaces where this would otherwise be impossible. Hemostatic mattress sutures along the cut margin of the liver are useful in controlling bleeding. Adequate mobilization of the liver through division of the ligamentous attachment to the diaphragm is an important aid. Temporary compression of the hilar structures, as I did in my case, is very helpful in controlling bleeding. This maneuver is also useful because grasping the hilum between one's fingers permits one to deliver the lobe better into the operative field and to restrict its motion during the resection. Altogether the problem of re-

section is not so difficult as one might expect it to be, and if care is used the procedure is apt to be attended by little hemorrhage.

It should be emphasized that one should never cut into the tumor itself nor even aspirate it, for such maneuvers have proved fatal on several occasions. In Leech's case[42] the tumor was tapped; there was severe bleeding, sutures were ineffective, only tearing the tumor and causing more bleeding, and the patient died in two hours. M'Weeney[46] incised the tumor, which bled profusely, and although the patient rallied from the severe hemorrhage, he died a week later of hematemesis. Ljunggren[40] punctured the tumor, and free bleeding resulted. He was able, however, to proceed with resection and recovery ensued. Cripps[13] also caused severe bleeding by incision into the tumor but was able to do a resection, and his patient survived.

A very real danger associated with hemangioma of the liver is rupture of the tumor. Dahle[15] reports a case diagnosed erroneously as acute appendicitis in which a hemangioma of the liver had ruptured. At the time of operation there was no longer any active bleeding although there was blood in the peritoneal cavity. The tumor was packed and recovery ensued. Tinker[72] found an actively bleeding hemangioma of the liver in a patient who had right lower abdominal pain and tenderness. A resection was done and the patient recovered. Others, however, were not so fortunate. Karp[31] had a patient in whom there was a spontaneous rupture, who was thought by the family doctor to have a ruptured tubal pregnancy. Because of a palpable mass the diagnosis was changed before operation to a cystic tumor of the liver. At operation the tumor was packed, and the patient died on the tenth postoperative day. Marckstadt[43] had a patient in whom there was spontaneous rupture of an hepatic hemangioma, diagnosed before operation as peritonitis; the tumor was packed at operation and the patient died in two days. Pozzi's patient,[57] who had a spontaneous rupture of a hemangioma, died two hours after exploration. Freund's patient[10, 61] apparently suffered a spontaneous rupture during the exploration and died in one hour. Hammer[25] reports the death of a 7-day-old infant which was apparently due to a spontaneous rupture of a hemangioma of the liver, and Kissinger and his co-workers[33] report the same accident in a 3-day-old child. Leflaive[39] describes another case of a patient who had apparently bled from a hemangioma of the liver and at autopsy was found to have peritonitis. Several other similar autopsy cases are mentioned in the literature.[43, 59]

From these experiences it is evident that spontaneous rupture of a hemangioma is a very real danger, that such tumors should never be incised or punctured at operation, and that if bleeding from a hemangioma occurs, better results may be expected from resection than from packing.

In contrast to the single death in 56 cases in which resection was done, there were 5 deaths among the 11 cases in which the tumor was not re-

moved at operation. An important factor in all of these deaths was the spontaneous rupture of the tumor before, during, or after operation, or bleeding from tapping or incising the tumor at operation.

Two patients have been treated with considerable success with x-ray therapy; 1 had an inoperable tumor of the right lobe,[58] the other a tumor in the right lobe several months after a hemangioma of the left lobe had been resected.[45]

In general, those patients who have undergone resection have done well. The postoperative course has ordinarily been smooth and not unduly long. Prolonged drainage has been unusual, and except in a few cases there has been no significant biliary drainage. The ultimate results have been good, most reports stating that the patient remained well. A number of patients were entirely well when seen one and one-half to two years after operation,[11, 36, 62, 67, 72] and Beck's patient was well ten years after operation.[4] Siebner's patient[67] had to have a repair of postoperative hernia two years after resection, but had been relieved of the symptoms of which she had complained. Perthes' patient,[54] a 6-year-old girl who underwent resection of the entire left lobe, died ten months later with ascites and dyspnea. Autopsy permission was not obtained. In several other instances the entire lobe has been removed and the patients have remained well.[20, 52, 65] The patient reported by Nossen[51] was well after operation but died in two years of carcinoma of the rectum. At autopsy there were seen several angiomas of the liver, and the author concluded that they must have been multiple at the time of operation. As I have stated before, the patient reported by Razemon and Decoulx[59] was not relieved after excision of the hemangioma until she returned some months later and underwent a cholecystectomy. Two months after Morris[45] resected a hemangioma of the left lobe the patient returned with a mass in the right lobe which was treated successfully with x-ray. My patient has not obtained complete relief. Such difficulties were few, however, and most of the patients reported in the literature were apparently entirely relieved of their complaints by resection of the tumor.

SUMMARY

Hemangiomas occur more commonly in the liver than in any other internal organ. They are usually small and asymptomatic, but occasionally they grow to sufficient size to cause symptoms. The disease affects females more often than males. It is found in all age groups but is especially common in the third, fourth, and fifth decades. The symptoms, other than those of the tumor mass itself or abdominal swelling, are due to pressure on other organs by the mass and vary with the location of the tumor. All lobes of the liver give rise to these tumors, but the left lobe more commonly than the others. About one-half the patients with hemangioma of the liver who seek surgical aid have their attention called to the condition by the presence of a tumor mass or by enlargement of the abdomen. The commonest symptoms which subsequently develop

are upper abdominal distress and gastrointestinal complaints, and such complaints initiate the illness in almost one-half the patients. These symptoms are such as to make one think first of some chronic gastric or duodenal lesion, but almost invariably by the time the patient presents himself for operative relief a tumor mass has become palpable which alters the diagnosis. In some patients the symptoms simulate biliary tract disease; in others they are more suggestive of an ovarian or uterine tumor. Spontaneous rupture of the tumor sometimes occurs, and this carries with it grave risk.

The correct diagnosis is difficult to make before operation. A mass is generally palpable and can ordinarily be identified as arising from the liver. There may be nothing characteristic about the tumor. Unusual compressibility or the presence of a bruit over the mass should make one suspect that the lesion may be a hemangioma. Sometimes a history of a peculiar buzzing or whirring sensation is of help in establishing the diagnosis. Gastrointestinal x-rays are frequently of considerable aid. Most commonly such studies demonstrate an extrinsic mass pressing upon the lesser curvature of the stomach, often lengthening it, and sometimes displacing the stomach downward and to the left.

When the tumor causes symptoms or presents a large asymptomatic mass, the treatment is resection. This procedure is ordinarily feasible and can be carried out with relative safety. One should never incise or aspirate the tumor as uncontrollable bleeding may occur. If there is bleeding from such a procedure or from spontaneous rupture, resection is preferable to packing. The postoperative course is ordinarily smooth and not prolonged, and the end results are good.

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SPLENECTOMY

A Method of Mobilizing the Spleen in the Presence of Dense Adhesions

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THE DIFFICULTY of removal of the spleen is directly proportional to the extent and density of the adhesions about it. Those bands near its anterior margin may be readily ligated and divided, but those posterior to its long axis cannot be properly visualized and must be torn or divided blindly. The most practical and most widely employed method of dealing with this difficulty is that popularized by W. J. Mayo. After all accessible adhesions have been ligated and divided, the remaining attachments are rapidly torn with the hand, the spleen is delivered into the wound, and the bed from which it has been lifted is quickly packed with very hot, moist gauze (Fig. 1). This is a very satisfactory method in most instances, but the adhesive bands usually contain large veins, and furious hemorrhage occurs and continues until the pack is in place and the splenic pedicle has been secured. If the adhesions are tougher than the capsule of the spleen, as is often the case, deep laceration of the organ occurs and another source of profuse bleeding is added. Until the spleen is completely delivered, neither packing of its bed nor control of its pedicle, which is the only effective method of controlling bleeding from the spleen, is practicable. Consequently, if the mobilization is not carried out rapidly, the hemorrhage may prove fatal before it can be controlled.

The adhesions may be extremely tough or there may be an almost complete fusion of the visceral and parietal peritoneum, either of which conditions may make it impossible to deliver the spleen rapidly by the usual method. Most authorities agree that under such circumstances it is best not to attempt splenectomy, and not a few surgeons, including myself, on at least one occasion have realized the wisdom of this view after it was too late.

Several procedures have been proposed for solution of the difficulty. Lanz and others have suggested ligating the splenic artery and leaving the spleen in place when removal is impracticable. Szendy ligated the entire pedicle and partially exteriorized and eviscerated the spleen, after which he packed the capsule tightly with gauze. Obviously these are more or less unsatisfactory substitutes for splenectomy.

Four years ago when confronted with the problem of removal of a spleen, the convex surface of which was completely fused with the parietal peritoneum, I devised, under the spur of necessity, a method of mobilization which has proved to be of distinct value.

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Procedure.—Any one of the incisions commonly used for splenectomy may be employed. My own practice has been to use a long, left mid-rectus hockey-stick incision which has always proved to be adequate. After the abdomen is opened, all accessible adhesions are ligated and divided. The anterior border of the spleen is retracted medially and the lateral margin of the wound is retracted laterally. This develops a fold of parietal peritoneum along the line of the attachment of the adhesions. With knife or scissors the peritoneum is divided just anterior to this fold, the incision extending the full length of the attachment (Fig. 2). This maneuver opens the relatively avascular areolar tissue

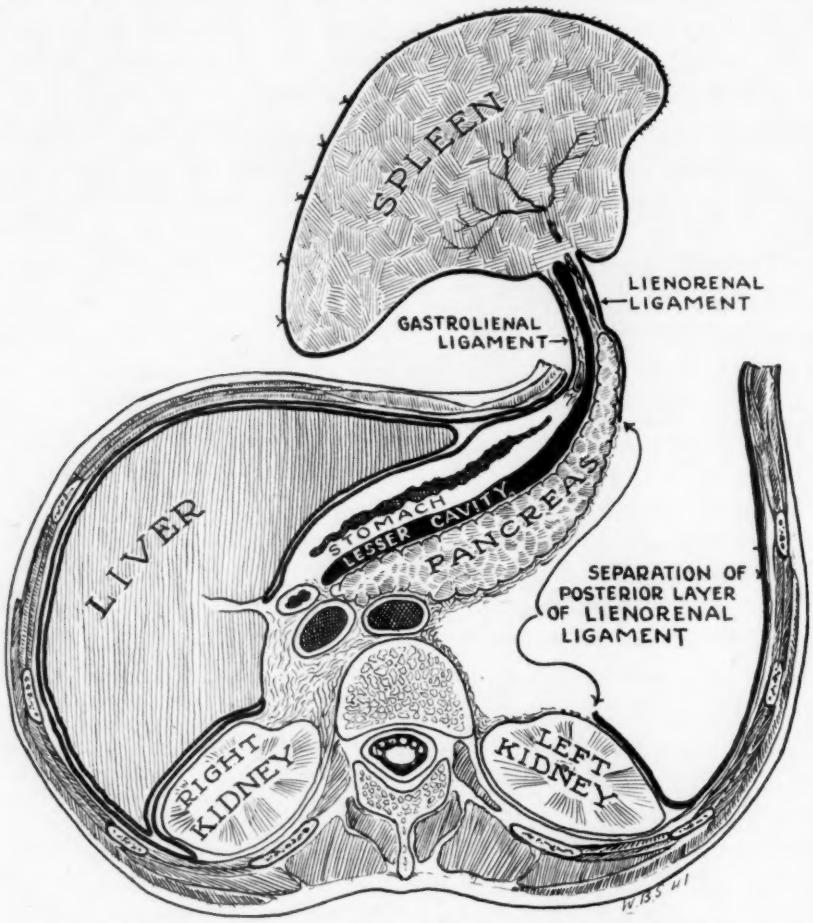

Fig. 1.—Condition after mobilization of spleen by usual method.

plane between the peritoneum and the transversalis fascia. The hand is then inserted into this plane and the dissection is rapidly extended, first posteriorly and then medially (Fig. 3), freeing the spleen from its bed and delivering it onto the abdominal wall still covered by the parietal peritoneum and the posterior layer of the lienorenal ligament (Fig. 4). Most of the blood vessels in the adhesions course within the structures removed with the spleen and consequently are not injured.

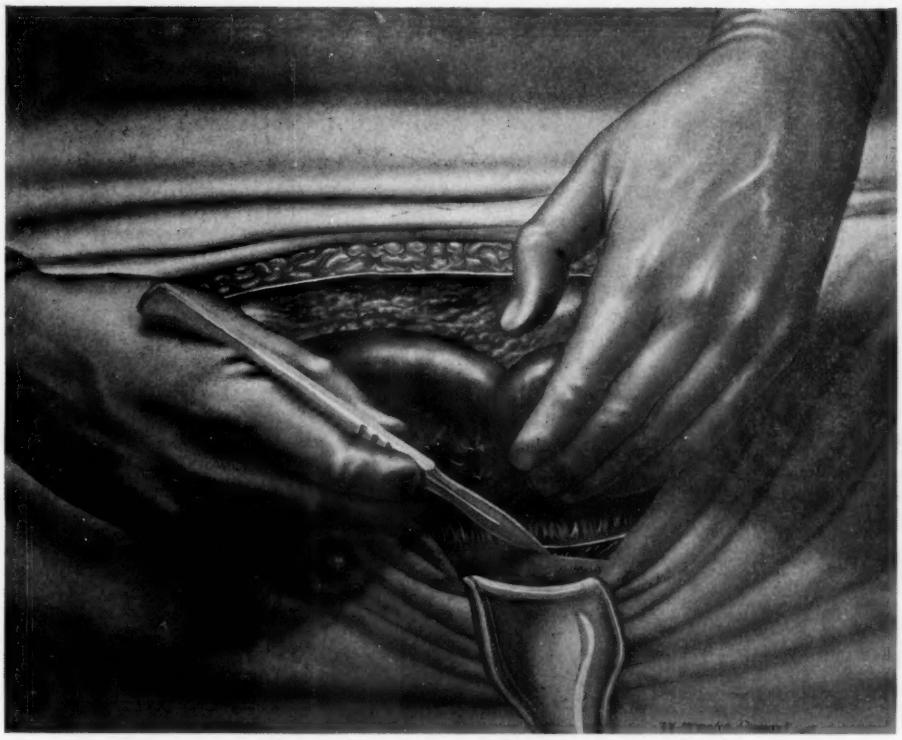

Fig. 2.—Incision of parietal peritoneum to open extraperitoneal space.

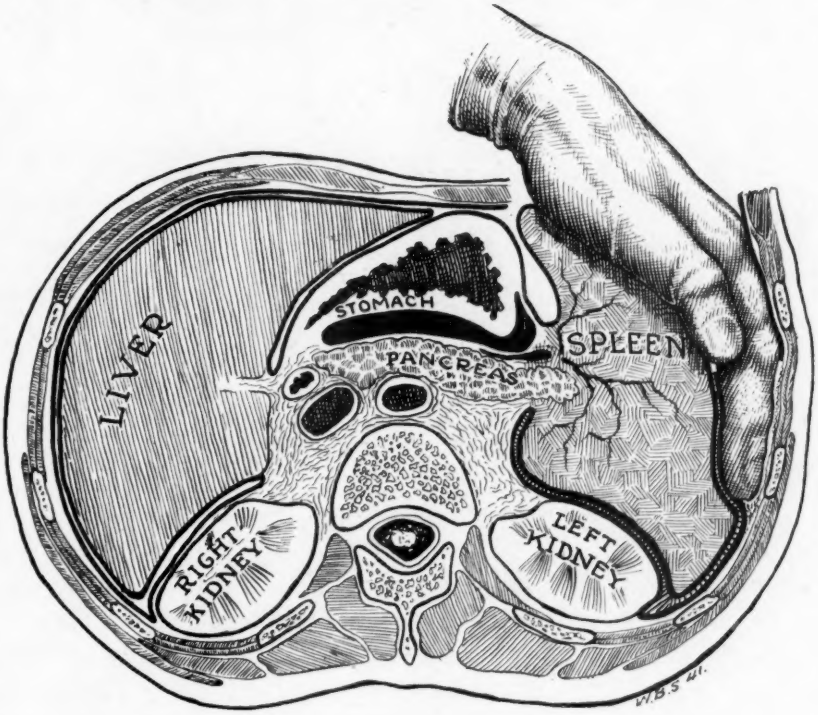

Fig. 3.—Detachment of parietal peritoneum with the spleen.

There is no danger of laceration of the splenic pulp, for no tension is applied to it, and it is protected from the dissecting fingers by two layers of peritoneum. The procedure is easily and quickly executed, for usually no fibrous bands are encountered. If bleeding from the denuded surface occurs, it is usually moderate in amount and is readily controlled by hot gauze packs. From this point on the operation is carried out in the same manner as if the spleen had been delivered by the conventional technique. The splenic pedicle is now completely exposed on

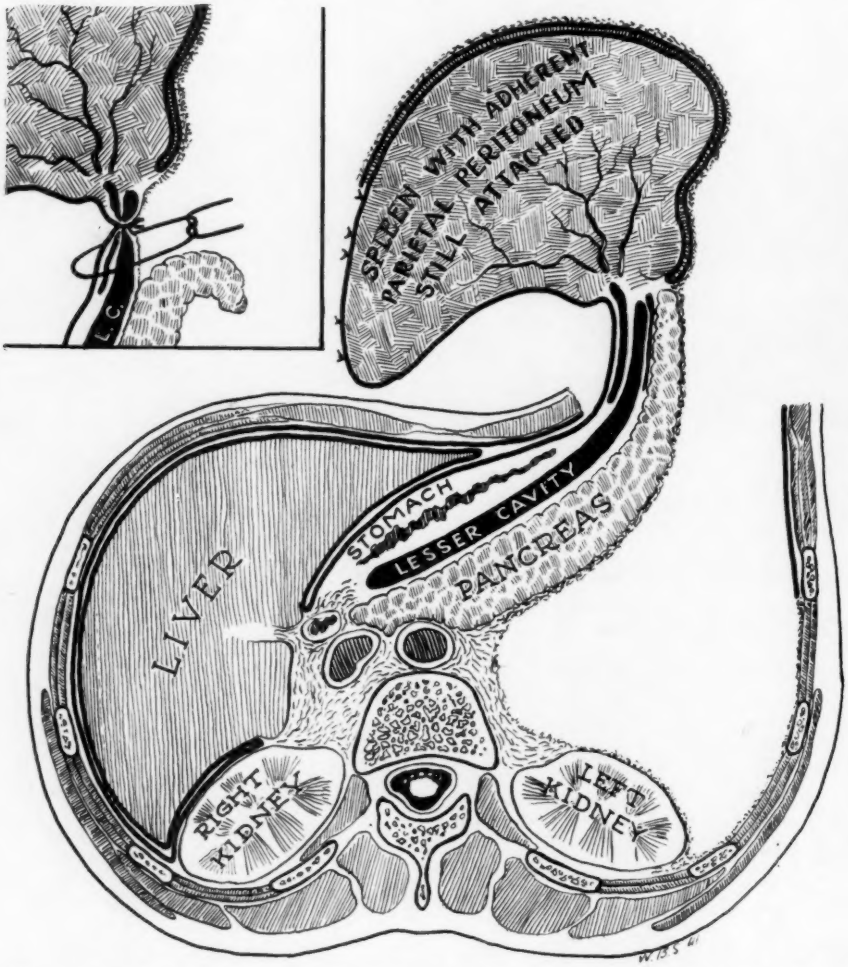

Fig. 4.—Condition after mobilization of spleen by Rives' method. *Insert.* Ligation of gastrosplenic and lienorenal ligaments together, preserving the integrity of the lesser peritoneal cavity.

its posterior aspect. The tail of the pancreas is identified and separated from the pedicle sufficiently to permit free exposure of the vessels. The pedicle is then controlled by a series of heavy catgut ligatures, the large size being selected not for greater strength but to prevent cutting through the very friable veins. It is my practice to pass the ligatures through the pedicle by means of a blunt forceps (Fig. 5). Not more

than two or three vessels should be included in each group, for centrally located vessels in large masses of tissue are likely to retract through the loop, thus loosening the ligature and permitting it to slip off. The gastrosplenic and the lienorenal ligaments are ligated together (insert, Fig. 4). This is simpler than handling the two separately and has the advantage of preserving the integrity of the lesser peritoneal sac, which prevents adhesion of the posterior surface of the stomach to the raw surface that has resulted from mobilization of the spleen. One must be very careful, of course, to avoid including a portion of the greater curvature of the stomach in the ligatures, an accident which may easily occur if the gastrosplenic ligament is very short. This is most likely to

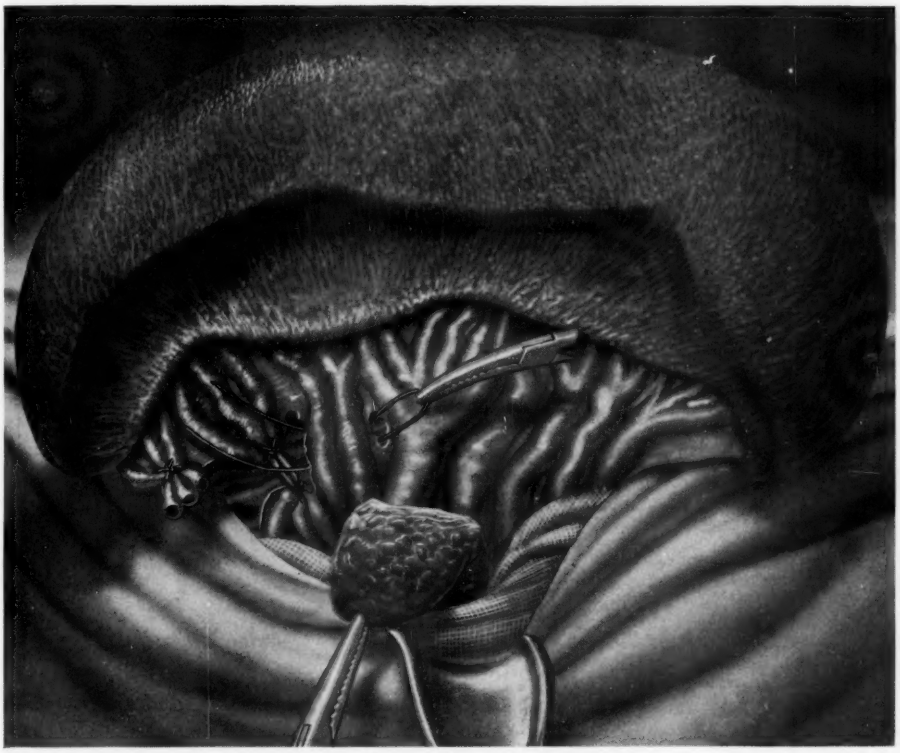

Fig. 5.—Ligature of splenic pedicle. Note that the external surface of the parietal peritoneum is exposed on the surface of the spleen.

occur at the upper margin of the gastrosplenic ligament where the vasa brevia are often extremely short. After the pedicle is carefully inspected for bleeding points and for injury to the pancreas or stomach, it is replaced in the abdominal cavity but is not fixed by sutures. It has been my experience that the ligated pedicle lies naturally in the desired position and that attempts to suture it in place are not only unnecessary but are likely to cause renewed hemorrhage from the pedicle due to puncture of the distended veins by the needle used in suturing. The remaining raw surface, which may be quite extensive, is covered by the omentum, which is turned up over the

colon and permitted to lie in the splenic fossa. This may be unnecessary because the adhesions that would result if this area were left uncovered would probably not be more extensive than those that occur after a splenectomy during which extensive adhesions have been forcibly torn with the hand. I have seen many examples of the latter that showed no evidence of disturbed gastric function postoperatively, although it is certain that the fundus of the stomach must have become firmly adherent in the region of the denuded surfaces. This portion of the stomach has only slight motility at best and fixation by adhesions probably interferes very little with its function.

SUMMARY

A procedure is described that makes splenectomy feasible and comparatively safe in instances in which the operation would be impossible by conventional methods.

WELCH BACILLUS INFECTIONS ARISING FROM THE STOMACH AND DUODENUM

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WELCH BACILLUS infections of the peritoneum and abdominal wall have been observed relatively frequently as complications of lesions of the lower intestinal tract.[1] On the contrary, lesions of the stomach and duodenum have rarely given rise to serious infection with the *Bacillus welchii.* A recent case observed on the Surgical Service of the New York Hospital led to a review of the literature for all cases of *Welch bacillus* infections secondary to lesions of, and operations on, the stomach and duodenum. Twelve such cases were found in the literature, and to this group two new cases are now added.

A brief review of Case 1 is given here, but a complete description of this case is given in a preceding paper.[1]

CASE 1.—G. G. (258992 N. Y. H.), a 52-year-old Spaniard, was admitted to the hospital in February, 1940, with a four months' history of abdominal pain, nausea, vomiting, and later chills and fever. Physical examination revealed an acutely and chronically ill man who showed marked evidence of weight loss. In the epigastrium a tender mass was palpated below a moderately enlarged liver. Following preparation with adequate fluids, an incision and drainage of an abscess of the lesser peritoneum was carried out. Culture of the pus yielded a pure growth of *B. welchii.* Postoperatively the patient developed gas gangrene of the abdominal wall which responded to incision and drainage with adequate débridement of the involved tissue and the local application of zinc peroxide. Sulfanilamide and sulfapyridine were used concomitantly with the above treatment. The gas gangrene of the abdominal wall was under control within four days; however, the patient's course was slowly downhill and he expired on the forty-third postoperative day.

Post-Mortem Examination.—At post-mortem (9942), a mucinous carcinoma of the pancreas with extension into the duodenum, and with perforation and invasion of a diverticulum of the stomach resulting in a perforation into the lesser peritoneal cavity was found. In addition, there was a direct extension of the inflammatory process into the liver with the formation of multiple large abscesses.

A second case of *B. welchii* infection of the peritoneum followed an operation on the stomach.

CASE 2.—S. R. (174259 N. Y. H.), a white man, aged 52 years, was admitted to the hospital in July, 1937, with a six months' history of symptoms attributable to a gastric ulcer. Following the usual preoperative preparation, the patient was subjected to a Billroth II type of subtotal gastric resection, and a large gastric ulcer, which had perforated into the body of the pancreas, was removed. On the first day after operation the patient developed signs of generalized peritonitis with

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TABLE I

GAS GANGRENE INFECTIONS IN LESIONS OF STOMACH AND DUODENUM

AUTHOR	YEAR	NO. CASES	AGE	SEX	DIAGNOSIS	OPERATION	WELCH BACILLUS INFECTION†		CULTURES		RESULT
							PERITONEUM	ABDOMINAL WALL	PERITONEUM	BLOOD STREAM	
Welch and Flexner[2]	1896	1	–*	F	Perforated cancer duodenum	None	I.	O.	*B. welchii*	–	Death
Flexner[3]	1898	1	–	–	Perforated gastric ulcer	None	I.	O.	*B. welchii*	–	Death
Pratt and Fulton[4]	1900	1	23	M	Perforated gastric ulcer	Laparotomy	I.	O.	–	–	Death
Page[5]	1900	1	32	M	Perforated gastric ulcer	None	I.	O.	*B. welchii*	*B. welchii*	Death
Welch[6]	1900	1	–	–	Perforated gastric ulcer	–	I.	–	*B. welchii*	–	Death
Welch[6]	1900	1	35	M	Perforated gastric ulcer	–	I.	–	*B. welchii*	–	Death
Learmonth[7]	1924	1	35	M	Perforated gastric ulcer	Resection of ulcer	I.	O.	–	–	Death
Dayton[8]	1925	1	18	M	Perforated gastric ulcer	None	I.	O.	*B. welchii*	*B. welchii*	Death
Douglas[9]	1931	1	–	–	–	Gastric operation	I.	I.	*B. welchii*	–	Death
Plath[10]	1934	1	31	M	Perforated gastric ulcer	Laparotomy	I.	O.	–	–	Death
Flynn[11]	1936	1	–	–	Carcinoma of stomach	Gastric resection	I.	O.	*B. welchii*	–	Death
Eliason, Erb, and Gilbert[12]	1937	1	–	–	Peptic ulcer	Gastric resection	–	I.	–	–	Recovery

*– Not stated.

†*I.* Presence of infection; *O.* Absence of infection.

gas in the peritoneal cavity and large amounts of pus and pancreatic juice escaping through the wound. *B. welchii, B. coli,* and enterococci were recovered on culture on two occasions. The patient's course was rapidly downhill and death occurred on the fourth postoperative day.

Post-Mortem Examination.—At post-mortem (8987) a fistulous opening in the center of the wound was found to communicate with a localized abscess; on more extensive investigation this abscess was found to be only one of several collections of pus in the peritoneal cavity, cultures of which grew *B. welchii* and *B. coli.* Careful inspection and gentle pressure on the lines of suture of the gastroenterostomy caused the escape of gastrointestinal contents. The loops of bowel were loosely held together by fibrinous adhesions. There were focal areas of fat necrosis of the pancreas.

DISCUSSION

Table I summarizes 12 cases from the literature in which gas bacillus peritonitis or gas gangrene of the abdominal wall have been major complications in lesions of the stomach and duodenum. Nine of these cases had spontaneous perforations, while in 3 the complication occurred as a result of gastric surgery.

There undoubtedly have been many other cases which never have been reported in the literature, but the fact that such infections are so few is not surprising; cultures taken from the stomach or duodenum rarely show *B. welchii;* whereas, these organisms are common habitants of the lower portion of the small intestine and of the entire large intestine.[13]

Welch bacillus infections arising from the stomach and duodenum are almost universally fatal. In the 12 cases reviewed above, recovery is reported in only 1 case, the case of Eliason, Erb, and Gilbert. In their case infection of the abdominal wall followed resection of a peptic ulcer, but no details are given as to the pathologic process or the therapy.

Treatment of the underlying Welch bacillus peritonitis conforms to the usual therapy for generalized peritonitis; in addition gas bacillus antiserum and one of the sulfonamide derivatives should be used. If there is an associated gas gangrene of the abdominal wall, we believe that in addition to the above therapy, adequate incision and drainage, débridement and the use of zinc peroxide locally according to the technique of Meleney and Johnson[14] should be carried out.

SUMMARY

Welch bacillus infections arising from the stomach and duodenum are extremely rare and have been practically always fatal. The 12 cases reported in the literature are briefly reviewed and to the group 2 new cases are added.

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GAS GANGRENE OF THE ABDOMINAL WALL

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A SERIOUS and much dreaded complication in surgery of the gastrointestinal and biliary tracts is gas gangrene of the abdominal wall. Fortunately this is a relatively infrequent complication and occurs less often after operations on the stomach and duodenum than after those involving the lower intestinal tract. We have recently had the opportunity to study a moderately extensive *Bacillus welchii* infection of the abdominal wall which followed operative intervention for perforations of the stomach and duodenum. The rarity of this condition and the result of therapy in our case, we believe, justify reporting it in some detail.

CASE 1.—G. G. (258992 N. Y. H.), a 50-year-old Spaniard, was admitted to the Surgical Service of the New York Hospital on Feb. 22, 1940, complaining of malaise, abdominal pain, nausea, and vomiting.

Present Illness.—Four months before admission the patient first noted epigastric pain of low intensity occurring in short paroxysmal attacks, and two weeks later experienced a chill followed by fever, severe epigastric pain, nausea, and vomiting. He was hospitalized at that time in another hospital, where a moderate anemia and melena were noted, but because of negative gastrointestinal x-ray studies, he was discharged without treatment. The abdominal pain which was dull and radiated laterally into the upper quadrants and which was associated with nausea and vomiting continued during the following two months. Anorexia, obstipation, daily fever, loss of weight, and several shaking chills were prominent features during the two months preceding admission.

Physical Examination.—The patient was a thin man who gave unmistakable evidence of considerable loss of weight and appeared both chronically and acutely ill. There was relative dullness to percussion over the right chest below the fifth rib posteriorly and in the axilla with diminution of breath sounds and of tactile fremitus over the same area. The epigastrium appeared full and palpation revealed an exquisitely tender mass in that region. The edge of the liver extended two fingerbreadths below the costal margin in the right midclavicular line and was very tender to pressure.

Laboratory Findings.—While the urine on admission was found to contain a moderate amount of albumin, with occasional erythrocytes, polymorphonuclear leucocytes and granular casts, subsequent specimens were clear. The hemoglobin was 11.9 Gm. per 100 c.c.; red blood cells, 4.3 million per centimeter; white blood cells, 33,500; icteric index, 15; plasma prothrombin, 52 per cent of normal; blood culture, negative.

Course and Treatment.—Following adequate administration of parenteral fluids, the laparotomy was performed through a right-rectus incision on the third day

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after admission and approximately 200 c.c. of pale greenish gray purulent material was drained from an abscess of the lesser peritoneum. The wound was closed around drains with through-and-through silver wire sutures.

Following operation the patient became jaundiced and developed a bronchopneumonia of the left lower lobe which was treated with sulfanilamide and sulfapyridine from the second to the seventh postoperative days. The wound continued to drain moderate amounts of pus which, like that drained from the abscess, yielded a pure culture of *B. welchii*. On the fifth postoperative day a diffuse erythema of the skin over the upper abdomen and lower thorax appeared, the area involved being extremely tender and crepitant. Counterincisions were made at the lateral and superior borders of the inflamed area and the wound was laid open, exposing the liver and the transverse colon. Local applications of zinc peroxide, as recommended by Meleney and Johnson,[18] were used and within four days there was marked improvement in the appearance of the skin of the abdominal wall with decrease in redness, tenderness, and crepitation. No recurrence or spread of the infection occurred, although the wound itself continued to drain pus containing *B. welchii*. In spite of the improvement in the abdominal wall infection, the patient's course was slowly but progressively downhill and was characterized by spiking temperature, chills, jaundice, and tenderness over the right lower thorax. Methylene blue, administered orally, was recovered in the drainage from the wound in less than eight hours. Sulfapyridine on the thirty-sixth to fortieth days after operation had no apparent effect on the condition of the patient, and on the forty-third postoperative day, pus was aspirated from the liver. A small incision into the liver revealed a large abscess cavity which was drained, but this procedure was of no avail and the patient died within three hours.

Post-mortem Examination.—The autopsy (9942) was performed two hours after death. In the epigastrium and right hypochondrium, a large granulating area surrounded by normal skin was present. A small ostium, from which purulent material could be expressed, lay in the center of the granulating wound and communicated with a sinus tract which extended 9 or 10 cm. into the liver. The peritoneal cavity contained 500 c.c. of clear, bile-stained fluid. The transverse colon, stomach, gall bladder, and liver were loosely adherent to the anterior abdominal wall and to each other, while the peritoneal surfaces elsewhere were smooth and shining. The liver was large (2,500 Gm.), fluctuant and its external surface was pale red-brown and covered by fine fibrinous adhesions. The sinus tract extended into the substance of the liver where it was in communication with another tract which extended into the lesser peritoneal cavity. In communication with these tracts were many areas in which the liver substance was completely destroyed and replaced by abscesses containing very foul green pus (*B. lactis aerogenes, B. welchii* and nonhemolytic *Streptococcus zymogenes*). The biliary ducts were patent and there was no evidence of thrombophlebitis of the portal vein. The pancreas was replaced by alternating areas of gray mucinous material and extremely hard tumor mass. Direct extension of the tumor tissue into the ampulla of Vater and the adjacent duodenal wall had brought about a perforation 1.5 cm. in diameter just superior to the papilla without causing obstruction to the flow of bile. The tumor also extended upward into the lesser peritoneal cavity where there was a localized accumulation of the same mucinous material and pus (*B. coli communis, B. pyocyaneus, B. welchii,* nonhemolytic *Str. zymogenes*). A small diverticulum-like pocket on the lesser curvature of the stomach was perforated and extended into the abscess of the lesser peritoneal sac. Thus, the stomach, duodenum, and liver were in communication with the abscess of the lesser peritoneal cavity; through the sinus tract in the liver, the abscess communicated with the abdominal wall.

Microscopic Examination.—Sections of the pancreas contained focal islets of apparently normal tissue, but most of the parenchyma was replaced by mucinous

carcinoma, obviously of pancreatic origin. The stomach wall was invaded only at the tip of the diverticulum-like pocket. No tumor cells were found in the liver, but there was a massive destruction of hepatic cells with abscess formation. The portal areas which were extensively infiltrated by plasma cells and lymphocytes showed no inflammation of the biliary ducts while the liver cells contained large quantities of yellow pigment. No evidence of gas gangrene was present in sections of skin and muscle taken from the edges of the wound.

Diagnosis.—Mucinous carcinoma of the pancreas with advanced fibrosis; extension of carcinoma into the ampulla of Vater, into the duodenum with perforation, and into the lesser peritoneal cavity; invasion of the tip of a diverticulum-like pocket of the stomach by tumor with perforation into the lesser peritoneal cavity; localized peritonitis with extension of inflammatory process into the liver; formation of multiple large abscesses and massive necrosis of the liver; wounds of laparotomy for drainage of lesser peritoneal cavity with sinus tract into the liver and lesser peritoneal cavity; granulating wounds of abdominal and thoracic wall (*B. welchii* infection of abdominal wall); jaundice.

In 1934 Orr[1] collected all reported cases of gas gangrene of the abdominal wall and found only 18 which he considered acceptable; to these he added 3 cases of his own, all of which were secondary to operations on the intestine and in all of which the patients died. In addition to Orr's series, 1 other case was found reported by Douglas in 1931.[2] Since Orr's report 30 additional cases have been described in the literature, bringing the total to 52. Table I gives a summary of the pertinent data concerning these 52 cases.

Besides the case of *B. welchii* infection described at length above, there have been three cases of gas gangrene of the abdominal wall at the New York Hospital in the past eight years. The histories of the three additional cases are as follows:

CASE 2.—M. G. (178968 N. Y. H.), a 49-year-old white woman, was admitted to the Surgical Service of the New York Hospital on Aug. 15, 1937, complaining of abdominal pain and vomiting of sixty hours' duration.

Past History.—Seven years before admission the patient had a left inguinal hernioplasty. At that time she was in the second month of pregnancy. Five months later she suffered an attack of distention, generalized abdominal cramps, and vomiting. Spontaneous premature labor occurred twenty-four hours later. The patient was acutely ill and a laparotomy was performed, generalized peritonitis being discovered. Three weeks after operation an abscess presented in the right lower quadrant which was incised and drained; this was followed by an uneventful recovery. The patient continued to have occasional attacks of abdominal pain and a tendency to constipation.

Present Illness.—The patient considered herself well until two and one-half days before admission at which time she developed severe cramplike pains and vomiting. She had a bowel movement at the onset of symptoms and an effectual enema on the day of entrance into the hospital.

Laboratory Findings.—Hemoglobin, 17.5 Gm. per cent; white blood cells, 8,400; Kline test, negative; blood urea nitrogen 12 mg. per cent.

Course and Treatment.—Conservative therapy was instituted for the first twenty-four hours, but because of continued abdominal pain, the failure to pass stool or flatus, and continued fecal return by way of Wangensteen suction, an exploratory laparotomy was performed. The entire small intestine was found to be dilated except for a few centimeters near the ileocecal valve; numerous adhesions between

TABLE I

GAS GANGRENE OF ABDOMINAL WALL IN LESIONS OF INTESTINES

AUTHOR	YEAR	CASES	NO.	DIAGNOSIS	OPERATION	THERAPY	RESULT
Ochsner and Schmidt[3]	1925	1		Appendical abscess	Appendectomy with drainage	Hydrogen peroxide and Dakin's irrigations	Recovery
Butler[4]	1926	2	1.	Appendical abscess	Appendectomy with drainage	Multiple incisions and drainage	Recovery
			2.	Intestinal obstruction	Cecostomy and lysis adhesions	Incisions and drainage Dakin's irrigations	Death
Lamprecht[5]	1928	1		Appendical abscess	Drainage	Antitoxin	Death
Shearer[6]	1929	1		Gangrenous appendix	Appendectomy	—*	Death
Butler and Rhodes[7]	1930	2	1.	Intestinal obstruction	Enterostomy	Antitoxin	Recovery
			2.	Strangulated ventral hernia	Enterostomy	Incision and drainage, antitoxin, Dakin's irrigations	Death
Eckhoff[8]	1930	7	1.	Chronic appendicitis	Appendectomy	Incision and drainage, Dakin's irrigations	Death
			2.	Inguinal hernia	Hernioplasty	Antitoxin	Recovery
			3.	Intestinal obstruction	Cecostomy	—	Death
			4.	Intestinal obstruction	Colostomy	None	Death
			5.	Acute appendicitis	Appendectomy	Incision and drainage, Flavine percolation	Recovery
			6.	Intestinal obstruction	Ileostomy	None	Death
			7.	Inguinal hernia	Hernioplasty, appendectomy	Flavine irrigations, antitoxin	Recovery
Douglas[2]	1931	2	1.	—	Gastric operation	—	Death
			2.	Appendical abscess	Drainage abscess	Antitoxin	Recovery
King[9]	1931	1			Appendectomy	Antitoxin	Recovery
Miyamoto[10]	1932	1		Appendicitis	Appendectomy	—	—
Traver[11]	1933	1		Appendical abscess	Drainage	Multiple incisions and drainage	Death
Orr[1]	1934	3	1.	Appendical abscess Intestinal obstruction	Drainage, enterostomy	—	Death
			2.	Femoral hernia, strangulated	Reduction, enterostomy	—	Death
			3.	Intestinal obstruction†	Enterostomy	—	Death
Kelly[12]	1933	1		Strangulated hernia	Operation (type not indicated)	Antitoxin	Death

*—Not stated.

†At operation a perforation at site of obstruction with generalized peritonitis was found.

Nason and Starr[13]	1934	1	Carcinoma of cecum	Resection and enterostomy	—	Death
Gamble[14]	1935	12	1. Gangrenous appendix	Appendectomy and drainage	Incisions and drainage	Recovery
			2. Appendical abscess	Drainage	Incision and drainage	Death
			3. Acute cholecystitis	Cholecystostomy	Incision and drainage	Recovery
			4. Chronic cholecystitis	Cholecystectomy and appendectomy	Incision and drainage	Death
			5. Intestinal obstruction	Enterostomy	Incision and drainage	Death
			6. Acute appendicitis	Appendectomy and drainage	Incision and drainage, antitoxin	Recovery
			7. Intestinal obstruction	Enterostomy	Incision and drainage	Recovery
			8. Acute cholecystitis	Cholecystostomy	Incision and drainage, antitoxin	Death
			9. Intestinal obstruction	Enterostomy	Incision and drainage	Death
			10. Acute cholecystitis Chronic appendicitis	Cholecystostomy, appendectomy	Antitoxin	Recovery
			11. Acute cholecystitis	Cholecystectomy	Incision and drainage, antitoxin	Recovery
			12. Chronic cholecystitis	Cholecystectomy	Incision and drainage, antitoxin	Death
Carothers[15]	1935	1	Intestinal obstruction	Enterostomy	—	Death
Howe[16]	1936	1	Chronic appendicitis	Appendectomy	Antitoxin	Recovery
Johnson[17]	1936	2	1. Appendical abscess	Drainage	Antitoxin	Recovery
			2. Gangrenous appendix, with perforation	Appendectomy, drainage	Antitoxin	Death
Meleney and Johnson[18]	1937	1	—	Cecostomy	Incision and drainage, zinc peroxide	Recovery
Eliason, Erb, and Gilbert[19]	1937	2	1. Peptic ulcer	Gastric resection	—	Recovery
			2. —	Gall bladder surgery (type not stated)	—	—
Lober[20]	1938	1	Acute appendicitis	Appendectomy	Incision and drainage, hydrogen-peroxide irrigation	Death
Coleman and Bennett[21]	1939	3	1. —	—	—	Death
			2. —	—	—	Death
			3. —	—	—	Death
Smith and Zimring[22]	1939	1	Perforated appendix	Appendectomy	Antitoxin	Death
Clute and Anglem[23]	1939	2	1. Cancer of colon, obstruction	Cecostomy	Incision and drainage, antitoxin	Recovery
			2. Cancer of colon, obstruction	Cecostomy	Incision and drainage	Recovery
Pérard[24]	1939	1	Appendical abscess	Drainage	Antitoxin	Death
Breslin[25]	1940	1	Subacute appendicitis	Appendectomy and drainage	Antitoxin	Death

the intestines were freed and an enterostomy carried out. The enterostomy tube began to function ten hours after operation and the patient passed fecal material by rectum. Eleven hours after operation the temperature rose to 40.1° C. per rectum with a comparable rise in pulse rate. Examination of the operative wound revealed extensive gangrene of the edges with marked tenderness and crepitation. Smears and cultures revealed the presence of *B. welchii, B. coli, B. lactis aerogenes* and enterococci. The abdomen was markedly distended and diffusely tender. Débridement of the abdominal wall was followed by irrigation of the wound with hydrogen peroxide; prontosil was administered intramuscularly and intravenously. The patient's temperature rose to 41.8° C. and in spite of therapy she died in coma sixty hours after operation.

Post-mortem Examination.—The examination (9014 N. Y. H.), two hours after death, revealed everted, necrotic borders of the wound with a fibrinopurulent exudate at its base and 100 c.c. of thin, fibrinopurulent fluid in the peritoneal cavity with loops of bowel loosely adherent to one another. In the jejunum, ileum, and ascending colon were many areas of submucosal hemorrhage and edema, while the mucosa of the colon was thick and velvety. An area of ulceration in the jejunum had a necrotic center which extended into the muscularis. The inflammatory process involved the entire bowel wall including the serosa.

Case 3.—C. A. (225746 N. Y. H.), a 72-year-old man, was admitted to the Surgical Service of the New York Hospital complaining of pain in the abdomen, cramplike and worse in the right lower quadrant, of two weeks' duration. Moderate anorexia and increased fatigability had been noted but there had been no change in bowel habit.

Physical Examination.—This revealed a dome-shaped abdomen in which loud borborygmi could be heard with each bout of cramplike pain; in the right lower quadrant there was a hard, round, immobile mass which was not tender. On rectal examination a firm mass could be felt over the promontory of the sacrum and the prostate was approximately three times its usual size.

Course and Treatment.—A flat plate of the abdomen gave evidence of marked distention of the intestine and stomach, and x-ray examination following barium enema showed an obstructive lesion with an irregular filling defect of the sigmoid. On the second hospital day a laparotomy was performed through a right McBurney incision and an abscess was found containing fecal as well as purulent material. Two perforations of the bowel, one of the ileum and the other of the cecum, connected with the abscess. The hard wall at the site of perforation was biopsied and found to be carcinoma. The abscess pocket was drained. On the second postoperative day the borders of the wound were indurated, crepitant, and tender, and culture of the wound revealed *B. welchii* and numerous other organisms. The lesion spread rapidly, involving the entire trunk as high as the midthorax, and the left thigh down to the knee. The temperature remained between 39 and 40° C. per rectum and the patient expired on the fourth postoperative day.

Post-mortem Examination.—(9670 N. Y. H.), a deep purplish red discoloration of the skin with induration and crepitus extended from the midthorax to 8 cm. below the left patella, and *B. welchii, B. coli, Staphylococcus aureus,* and fusiform bacilli were cultured from the lesion of the abdominal wall. The cecum, ileum, sigmoid, colon, and urinary bladder were all firmly adherent to one another and there were two perforations in the wall of the bowel just proximal and distal to the ileocecal valve. The adjacent wall was thickened and infiltrated by tumor cells. The perforations were in direct communication with a localized peritoneal abscess which, in turn, was draining freely through the abdominal wall. In the sigmoid colon was a cauliflower growth 4 cm. in diameter, the surface of which was ulcerated, forming a craterlike depression which had perforated and was in continuity with the lesions of the ileocecal region. *B. welchii* and *B. coli* were cultured from the heart's blood.

CASE 4.—H. F. (83455 N. Y. H.), a 42-year-old white woman, was admitted to the hospital complaining of cramplike abdominal pain, fever, and weakness.

Past History.—In 1935, following a five-day history of obstipation, abdominal cramplike pain, and distention, the patient was admitted to the hospital where an obstructing carcinoma of the sigmoid was diagnosed and removed following preliminary colostomy. An end-to-end anastomosis of the colon was carried out.

Present Illness.—The patient remained well until August, 1940, when she was admitted with the history of increasing constipation, abdominal cramplike pain, and weakness for two months.

Physical Examination.—This revealed a chronically and acutely ill woman who had a hard, tender mass in the left lower quadrant extending from the left midaxillary line to the middle of the abdomen.

Laboratory Findings.—Hemoglobin, 4.9 Gm.; red blood cells, 2.8; and white blood cells, 24,700.

Course and Treatment.—On the seventh hospital day an exquisitely tender, erythematous area developed in the left groin. Following the application of hot wet dressings, an incision released 10 c.c. of foul-smelling pus containing gas bubbles. Culture of the pus revealed *B. welchii*, *B. coli*, and a beta-hemolytic streptococcus. Within the next two days the infection spread rapidly to invade the abdominal wall, extending to the midline, to the costal margin, to the left flank, and down to the middle of the left thigh. Crepitation, marked tenderness, and a pinkish red color of the skin were prominent features. The patient was taken to the operating room where multiple incisions were carried down to the deep fascia which was found to be undergoing liquefaction. A point of perforation was found which extended to the tumor mass in the region of the descending colon. Postoperatively the wound was treated with hourly irrigations of hydrogen peroxide through Dakin's tubes during the day and each night with zinc peroxide dressings. Within seven days the wounds were entirely clean and there was no further spread of the infection. However, the patient's general course was downhill and she died on the twenty-first postoperative day.

Post-mortem Examination.—(10103 N. Y. H.), a recurrent carcinoma of the pelvic colon was found with extensive necrosis and generalized fibrinopurulent peritonitis. There was a moderate degree of fatty degeneration of the liver.

DISCUSSION

Although Welch bacillus infection of the abdominal wall may complicate any operative procedure, it most commonly follows surgical intervention for suppurative appendicitis or for intestinal obstruction. In

TABLE II

POSTOPERATIVE GAS GANGRENE OF ABDOMINAL WALL

OPERATIVE PROCEDURES	NO. OF CASES
For appendicitis (appendectomy, drainage, appendectomy and drainage)	21
Enterostomy	11
Cecostomy	5
Gall bladder surgery	5
Gastric operations	2
Colostomy	1
Appendectomy with cholecystectomy	1
Appendectomy with cholecystostomy	1
Hernioplasty (inguinal)	1
	48*

*Operative procedures not mentioned in 4 of the 52 cases.

Table II we have listed in the relative order of their occurrences the surgical procedures which have been followed by gas gangrene of the abdominal wall in 48 of the 52 reported cases.

Although gas gangrene of the abdominal wall is such an infrequent complication of gastrointestinal surgery, the mortality is high, 60 per cent in the collected cases, which makes it extremely desirable to discover effective therapeutic measures for its treatment. Early recognition by the surgeon of this complication is essential. The onset of infection usually is manifested within thirty-six to seventy-two hours after operation, but this period may vary from a few hours to several days, depending largely on the virulence of the organism and the resistance of the patient.

The disease usually begins with an abrupt rise in pulse rate out of proportion to the temperature. There is every evidence of toxicity with general malaise, extreme prostration, restlessness, and perhaps, coma. This is associated with a moderate leucocytosis and usually with a rapid onset of secondary anemia. Marked increase of pain in the wound is often a prominent feature.

Locally the wound may reveal swelling, edema, redness, and especially acute tenderness. The skin at the margin of the wound becomes red, then dusky, progressing to an extremely dark color and finally to total gangrene. The often described sweetish, acrid, or "mousy" odor may be noted. Pressure on the margin of the wound produces a serosanguineous exudate in which bubbles of gas may be seen. Palpation of the surrounding tissues may produce a definite sense of crepitus. Smears taken from the exudate will almost invariably reveal numerous large gram-positive bacilli, and finally, anaerobic cultures lead to a positive diagnosis.

Four therapeutic agents have been suggested, two of which are systemic and two local. Gas bacillus antitoxin is said to reduce the mortality significantly but as yet there has not been sufficient experience at the New York Hospital to warrant any conclusions as to its value. Sulfanilamide was first used in gas gangrene of the extremities by Bohlman[26] in three patients, all of whom recovered. Sadusk and Manahan[27] reported two instances of *B. welchii* infection following abortion which were successfully treated with sulfanilamide. Bliss and Long[28] state that sulfanilamide has a bacteriostatic effect in experimental *B. welchii* infection in mice. Stephenson and Rosa[29] have compared the therapeutic value of sulfanilamide and sulfapyridine with that of *B. welchii* antitoxin in experimental infection in mice. They concluded that sulfapyridine and sulfanilamide were slightly more effective than the antitoxin when infection was produced by intraperitoneal injection of the Welch bacillus, while sulfanilamide and sulfapyridine were of little or no value when an intramuscular injection of a lethal dose of Welch bacilli was employed. The antitoxin, however, prevented death in all such animals.

Longacre and Honold[30] recently have compared the relative value of sulfanilamide, sulfapyridine, sulfathiazole, and sulfamethyl-thiazol in experimental gas gangrene in guinea pigs, and made two significant observations: (1) that in no instance would any of these chemotherapeutic agents protect the animal completely when a moderately large inoculation of a strain of *Clostridium welchii* was injected into the thigh muscles, but that there was slight prolongation of life and this was noted particularly in those animals treated with sulfathiazole and sulfamethylthiazole; (2) that the pathologic changes in the muscle of the animals treated with the latter two drugs were much less advanced, both in intensity and in the extent of the spread, than in the sulfanilamide and sulfapyridine treated animals. Swan[31] reported on the highly successful therapeutic results obtained in a series of cases of frank gas gangrene and others with wounds infected with anaerobic gas-forming organisms by the combined use of antigas gangrene serum and sulfanilamide. This author felt that both agents were of value and that they should be used concomitantly. Wilson[32] stated that in compound fractures of the extremities due to war injuries, sulfathiazole by mouth and the same agent applied directly to the wound after adequate débridement and in association with encasement in plaster practically eliminated the complication of gas gangrene.

Local x-ray therapy has been successfully employed by Kelly[12] and his findings have been confirmed by several other workers, but the method has not been generally accepted and none of our cases has been treated in this manner.

Local therapy with zinc peroxide was first reported by Meleney and Johnson[18] in 1937; they treated successfully one case of gas gangrene of the abdominal wall. Pearse[33] found zinc peroxide effective in the treatment of a *B. welchii* infection of an open wound which had failed to respond to treatment with x-ray and sulfanilamide. Johnson and Meleney[34] have demonstrated the effectiveness of zinc peroxide against the vegetative forms of *B. welchii* in vitro, but the spores were found to be relatively resistant. They also present evidence of the inactivation of the hemotoxin elaborated by the bacilli by zinc peroxide.

The first case described in this communication (G.G.) was given sulfapyridine and sulfanilamide from the second to the seventh postoperative days, and in spite of this therapy a moderately severe gas gangrene developed. After adequate counterincisions were made and the wound laid open, zinc peroxide therapy was instituted and within five days the infection was well under control. We believe the value of zinc peroxide in this instance is above question while the effect, if any, of the sulfanilamide and sulfapyridine is not clear. It is possible that they may have helped delay the onset or reduced the intensity of the infection, although certainly they were incapable of controlling the infection.

Another recent case of ours (Case 4) supports the efficacy of zinc peroxide in the treatment of these infections. Other than adequate wide-

spread incisions with débridement and drainage and irrigations with hydrogen peroxide, zinc peroxide was the only agent used. The rapid and complete control of the infection was more remarkable in view of the fact that no chemotherapeutic agent or gas gangrene antitoxin was employed.

It would seem advisable to treat any case of gas gangrene involving the abdominal wall with the local application of zinc peroxide according to the technique described by Meleney and Johnson, following the establishment of adequate surgical drainage and débridement. In view of the recent reports from England of the successful prophylaxis and treatment of gas gangrene by the combined use of gas gangrene antitoxin and chemotherapeutic agents, we feel that the gas gangrene antitoxin in combination with adequate amounts of sulfathiazole should supplement the local treatment.

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PERITONITIS*

III. Studies in Peritoneal Protection With Particular Reference to Action of Sulfonamide Drugs in Experimental Peritonitis

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IN 1928 we undertook the study of the protection of the peritoneum against infection, having in mind particularly the control of postoperative peritonitis after resections of the colon. We first studied by aerobic and anaerobic methods the peritoneal exudate obtained at operation from 106 human beings with peritonitis,[1] and found that many of the cases without perforation and all the cases with perforation yielded two or more varieties of organisms, if the culture grew at all. Some member of the coli group was nearly always present; next in frequency was some form of intestinal nonhemolytic streptococcus, and third, *Clostridium welchii*. The colon bacillus seemed by far the most important. Somewhat to our surprise the presence of *Cl. welchii* did not add materially to the severity of the infection. We later reported experiments[2] demonstrating that two or more of these species acting together may be more lethal in smaller numbers than when acting alone, as if their action were synergistic.

HISTORICAL

The study of peritoneal immunity or protection extends back at least to 1894, when Issaef[3] reported that serum, broth, urine, 2 per cent nucleic acid, and other substances, injected into the peritoneal cavity of guinea pigs, rendered them immune to cholera organisms injected a few days later. The degree of protection was not over fifteen times the dose that killed unprotected controls, but the evidence seemed to be clear that a number of different and unrelated substances would stimulate some protective mechanism within the peritoneal cavity. Klein[4] in 1893 had reported similar nonspecific protection achieved against cholera vibrios by the intraperitoneal injection of various other species. Pfeiffer[5-7] with Issaef also published in 1894 the series of experiments with cholera organisms that demonstrated what later came to be called the Pfeiffer phenomenon, a prompt lysis of the vibrios in the peritoneal cavity of immunized animals. Although this phenomenon was illustrated by the intraperitoneal injection of the cholera vibrios, its relationship to clinical peritonitis was hardly appreciated. In the Cavendish

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lecture in London in 1904, von Mikulicz[8] reported Miyake's experiments in which intraperitoneal and subcutaneous injections of various substances were shown to give protection against organisms of the colon group or intestinal contents introduced intraperitoneally afterwards. Von Mikulicz had used nucleic acid, neutralized, in 2 per cent strength subcutaneously in fifty-five human beings before abdominal operations, and was pleased with the postoperative course. He explained the beneficial effect by the leucocytosis which the nucleic acid called forth. He tried one intraperitoneal injection of this substance, but it caused so much distress that he did not attempt this route again. Solieri[9] in 1902, after experiments with guinea pigs, tried intraperitoneal injections of saline solution anteoperatively in man. Durham[10] in 1897 recommended the use of streptococcus serum against peritonitis, and Wilkie[11] in 1910 tried convalescent human serum with what he thought was benefit to his patients. Loeffler and Abel[12] in 1896 had demonstrated in guinea pigs specific protection against *Bacillus typhosus* and *Escherichia coli* by intraperitoneal administration of their specific antisera obtained from dogs. Makins and Sargent[13] in 1907 used polyvalent anticoli horse serum in human beings with peritonitis with questionable benefit.

In 1928, Herrmann[14] revived interest in peritoneal protection by obtaining a certain degree of peritoneal immunity by means of a mixed streptococcus and colon vaccine. Thereafter, Dixon and Bargen,[15] and, for a time, Rankin,[16] developed the clinical use of similar vaccines to produce peritoneal protection. Meanwhile Steinberg and Goldblatt,[17] and later Steinberg alone,[18] published their experimental work on dogs, during which they developed their product, bactragen, a composition of gum tragacanth, aleuronat, and the vaccine of a special strain of *E. coli*. This was used intraperitoneally to produce a sterile peritonitis and with it peritoneal immunity. This substance has received favorable comment after a clinical trial by Potter and Coller[19] and Coller and Ransom.[20] Johnson[21] and also Young and Marks[22] have tried and advocated the preoperative use of concentrated amniotic fluid, injected intraperitoneally. Many surgeons, chiefly in Germany, have recommended the use of sera from horses and cattle injected with *E. coli*.

THE NEED

The need for new means of preventing postoperative peritonitis in abdominal surgery is still great in spite of advances in surgical technique and pre- and postoperative care during the past decade. At the Presbyterian Hospital in the period 1933 to 1939 inclusive, 316 radical resections were done for carcinoma of the rectum and colon. The postoperative mortality in five of these years lay between 13 and 19 per cent, but two bad years raised the average to 20.3 per cent. This represents the work of the staff as a whole. One member, Charles L. Janssen, who did nearly one-half of the abdominoperineal resections for carcinoma of the rectum, had a mortality rate which was about one-

third that of the staff as a whole, and in the last three years of his life performed 27 of these operations with but 1 death. But the records of a few specially trained and gifted operators do not represent the difficulty experienced by the surgical profession the country over in preventing postoperative deaths after major operations on the intestinal tract.

We have tried to discover what part peritonitis played in this high postoperative death rate but found accurate estimation unobtainable. The diagnosis of postoperative peritonitis is frequently difficult while the patient is yet alive, and even at autopsy the role of any peritonitis found is often hard to appraise. The patients die usually with a complication of lesions. How many of them would have escaped or survived their pneumonia or ileus if they had not also had pus in their peritoneal cavity? A numerical answer cannot be given, but after reviewing the records with care, it is our impression that in one-half of the fatalities, at least, peritonitis was an important cause of death. It is still more difficult to estimate the increase of morbidity from peritonitis among the survivors, but undoubtedly it is a factor of primary importance.

CHARACTER OF THE ORGANISMS PRODUCING PERITONITIS

Apart from the rather specialized forms of peritonitis due to single organisms like the gonococcus, the pneumococcus, the hemolytic streptococcus, or the tubercle bacillus, most infections of the peritoneum are produced by inhabitants of the intestinal tract. The organisms most often obtained by culture of intestinal contents are *E. coli,* enterococci, and *Cl. welchii,* the same varieties that we found in our study of the peritoneal fluid of human beings with peritonitis. In 85 per cent of our positive cultures in that study, two or more varieties of organisms were found, illustrating that the infection is usually mixed. We have never obtained a strain of these organisms that was highly virulent for laboratory animals. At times, the virulence of *E. coli* could be enhanced by rapid passage through animals to a point where 10,000 would kill a 20 Gm. mouse, but this was not true of the enterococci or *Cl. welchii.* It was also impossible for us to maintain a constant virulence, so that experiments with the same strain performed on different days could not be compared. Most of the colon forms and the *Cl. welchii* were toxin producers. Some strains of the colon group developed two types of colonies; one, a dark opaque colony, was a toxin producer and relatively virulent; whereas, the other, a light colony, possessed neither of these properties. In addition to the toxins demonstrable in some of the filtrates, there was also a toxin present in the bacterial bodies of cultures that had been killed by heat or formalin. We were never able to evoke any peritoneal protection against injection of these dead bacterial bodies. This may be one reason why we could evoke so little protection against cultures of low virulence, because with them multiples of a lethal dose of living organisms soon approached the lethal dose of killed organisms.

PROTECTION EXPERIMENTS WITH MICE AND GUINEA PIGS

Our general procedure was to protect the animals, except the controls, by the intraperitoneal injection of various substances, and then test the degree of protection by injecting living bacteria into the peritoneal cavity in varying amounts, and noting how large a dose the protected animals would survive in terms of the doses that would kill the unprotected controls. The infecting organisms were injected as actively growing four- to six-hour cultures of *E. coli*, enterococci, or *Cl. welchii* singly or in combination; or freshly collected human or animal intestinal contents were strained through cotton to eliminate gross particles, and injected; or fresh cultures of intestinal contents were used. Before finally testing each protecting agent, it was necessary to find out in what amount it should be injected, how often, and at what intervals in order to achieve the best results. In general, we found that two injections, given about twenty-four hours and two hours before the bacteria, gave as good results as more numerous injections. The number of organisms injected was estimated by reading a sample from the culture flask by means of the Gates turbidimeter. Dilutions were then made directly from the flask for the largest doses and from them for the smaller doses. No experimental result was accepted unless it could be repeated.

Because of the wide individual variations among the animals in their susceptibility to infection and their response to the protecting agents used, it was necessary to check each dose of organisms by three animals instead of one. In this way, accidental deaths were less likely to confuse the significance of the experiment.

1. *Protection by Means of Living Organisms.*—Clinicians have believed for many years that the peritoneum is more resistant to infection at the time of a second laparotomy than at a first. Whether this is a true, local immunity has never been proved so far as we know. We attempted to study this phenomenon by inoculating guinea pigs intraperitoneally at weekly intervals with gradually increasing doses of living *E. coli*, enterococci, and *Cl. welchii*, the organisms we found most frequently in peritonitis in human beings. Of 16 guinea pigs receiving *E. coli communior*, in only 1 was immunity obtained sufficient to withstand 7.5 minimal lethal doses. Most of the other guinea pigs died of peritonitis during the process. Of 25 animals receiving *Cl. welchii*, only 1 reached an immunity of 12 minimal lethal doses, and it died subsequently of a smaller dose. All the others died of peritonitis or infections of the abdominal wall. Of 31 animals receiving streptococci, only 1 finally withstood 8 minimal lethal doses. Some of the animals received as many as 18 weekly injections. No agglutinins could be found in the animals that did achieve some immunity. It seemed clear from these experiments that immunization by means of living organisms, as we attempted it, at least, was associated with great risk and uncertainty and little hope of practical value.

2. *Protection by Filtrates.*—When intestinal bacteria are grown in a suitable fluid medium, the resulting bacterial emulsion may be centrifuged, and the supernatant portion passed through a Berkefeld filter to yield a clear fluid which is sterile except possibly for filtrable forms. The filtrate may contain among other things bacteriophages, the antivirus described by Besredka, and soluble bacterial products. Its acidity may differ from that of the original medium used. It is, therefore, a complicated fluid of uncertain and variable composition.

We prepared filtrates from various strains of the following: *E. coli,* enterococci, *Cl. welchii,* singly and grown together, human and animal intestinal contents taken from the ileum or parts of the large intestine, and cultures from similar intestinal contents. The filtrates were prepared from cultures grown aerobically or anaerobically. After testing for sterility, the filtrates were injected into guinea pigs or mice which subsequently received living organisms intraperitoneally.

Repeated experiments led to the following deductions. Intraperitoneal injection of filtrates gave better protection than subcutaneous injection. One injection given thirty-six to twenty-four hours before the bacteria, followed by a second injection eight to two hours before the bacteria, gave as good protection as did more frequent doses or doses given at other times. Filtrates administered after the injection of bacteria were of no value. Because the toxicity and potency of the filtrates varied, it was impossible to set a standard dose, but generally 1 c.c. for a 350 Gm. guinea pig and 0.05 c.c. for a 20 Gm. mouse were sufficient. Filtrates prepared from eight-day cultures were not consistently better than those prepared from twenty-four-hour cultures. Filtrates heated to 55° C. were far less potent than unheated. Freshly prepared filtrates were better than those that had been allowed to stand for several days. Rapidity of filtration and the porosity of the filter had no appreciable effect on the value of the filtrate.

It was further found that filtrates prepared from a virulent (dark) colony of *E. coli* almost always gave better protection than did those prepared from other organisms or combinations of organisms or from direct cultures of intestinal contents. Filtrates from avirulent (light) colonies of *E. coli,* on the other hand, were never observed to be potent. These facts held true no matter whether the filtrates were used for protection against *E. coli,* streptococci, *Cl. welchii* in pure culture, or the combination of all three, or intestinal contents or cultures of intestinal contents. We could not show that the *E. coli* filtrate protected better against homologous than against heterologous strains, but we did discover that the degree of protection, measured in minimal lethal doses, was far higher against virulent organisms than against organisms of low virulence.

The degree of protection obtained was often excellent and gave promise of real clinical value, as the following experiment illustrates (Table I).

TABLE I

EXPERIMENT 16.—GUINEA PIGS, WEIGHT 310 TO 370 GM., RECEIVED FILTRATE OF VIRULENT STRAIN OF E. COLI, GROWN IN PHOSPHATE BROTH FOR 8 DAYS, FOLLOWED BY LIVING E. COLI OF SAME STRAIN.

PIG NO.	FILTRATE INJECTED 12/6/29	FILTRATE INJECTED 12/7/29	ORGANISMS INJECTED 12/8/29	RESULT
1	0.5 c.c.	0.5 c.c.	12 billion	Died
2	0.5 c.c.	0.5 c.c.	6 billion	Lived
3	0.2 c.c.	0.2 c.c.	12 billion	Died
4	0.2 c.c.	0.2 c.c.	6 billion	Lived
5	Control		20 million	Died
6	Control		10 million	Died
7	Control		2 million	Died
8	Control		0.5 million	Died

Result: Protection for 12,000 minimal lethal doses, or more.

Later experiments, however, showed that a degree of protection comparable to this could be obtained only against the one organism that could be brought to a relatively low numerical minimal lethal dose, namely *E. coli,* and then only when the strain of *E. coli* protected against actually was virulent. As no strains were encountered that were virulent for animals when first obtained, until after repeated animal passage, we feared that the following experiment more truly represented the degree of protection that might be obtained clinically in human beings.

TABLE II

EXPERIMENT 62.—MICE 18 TO 22 GM. VARIOUS FILTRATES USED AS PROTECTING AGENTS AGAINST CULTURE OF E. COLI, ENTEROCOCCI, AND CL. WELCHII FROM PATIENT T. EACH MOUSE EXCEPT CONTROLS RECEIVED 0.05 C.C. OF DESIGNATED FILTRATE 26 HR. AND 2 HR. BEFORE INJECTION OF ORGANISMS

DOSE OF COMBINED ORGANISMS	FILTRATE (OLD) OF COMBINED COLI, ENTEROCOCCI, AND WELCHII (PATIENT T)	FILTRATE (NEW) OF COMBINED COLI, ENTEROCOCCI, AND WELCHII (PATIENT T)	FILTRATE (NEW) OF COMBINED COLI, ENTEROCOCCI, AND WELCHII (PATIENT L)	FILTRATE (NEW) OF STOOL CULTURE (PATIENT L)
10 billion	Died	Died	Died	Died
1 billion	Died	Died	Died	Died
100 million	Died	Lived	Lived	Lived
10 million	Lived	Lived	Lived	Lived
1 million	Lived	Lived	Lived	Lived
100 thousand	Lived	Lived	Lived	Lived
10 thousand				
	CONTROL NO PROTECTION			
100 million	Died			
10 million	Lived			
1 million	Lived			
100 thousand	Lived			
10 thousand	Lived			

Result: One minimal lethal dose protection shown for three of the filtrates, no protection shown for the old filtrate.

The experiments with filtrates forced us to conclude that while against virulent strains of *E. coli* good protection could be demonstrated, very little protection could be obtained against organisms whose virulence had not been artificially enhanced by animal passage. Furthermore, we

found that filtrates had the disadvantage of great variability in toxicity and potency, and that they degenerated rapidly. We therefore abandoned them.

3. *Protection With Sera.*—We tried first a horse serum prepared by a commercial laboratory from *E. coli* filtrates that we supplied. While, at first, samples of these sera injected intraperitoneally as prophylaxis against intestinal organisms gave promise of good protection, later tests did not confirm this. After several weeks of trial, this method of producing a potent serum was abandoned.

In our own laboratory, we obtained sera from rabbits that were injected over a period of several weeks intravenously with increasing doses of vaccines and filtrates of *E. coli,* streptococci, and *Cl. welchii,* singly and in combinations. The sera that by agglutination tests appeared to be potent against their antigens were then tested for their ability to protect mice or guinea pigs against infection by various intestinal organisms. As was to be expected from the work with filtrates, by far the best protection we were able to demonstrate was that afforded by the sera from rabbits which had been injected with *E. coli* vaccine (with or without *E. coli* filtrate) when used against virulent *E. coli.* The sera were given intraperitoneally approximately twenty-four hours and two hours before the organisms. Serum given after the organisms were injected did not appear to give much protection. Normal serum consistently gave little or no protection against any organisms and was abandoned as a control.

Experiment 38, which is shown in Table III, illustrates the results obtained. The serum used in this experiment was obtained after the injection of rabbits with *E. coli* vaccine alone. The intestinal contents were obtained from a mouse, emulsified in broth, and the cloudy supernatant fluid pipetted off for use. Similar results were obtained when intestinal contents from guinea pigs were used.

In summary, concerning the serum work, it may be said that while we did not test the sera as extensively as we did the filtrates, the protection afforded by both was roughly of the same degree. The sera, if potent, seemed less toxic and more reliable than the filtrates. To be effective, they had to be given prophylactically. The more virulent the culture, the greater their degree of protection in terms of minimal lethal doses. We made no tests regarding their specificity.

4. *Protection by Vaccines.*—The greatest part of our work was done with vaccines prepared from intestinal organisms singly or in combination. We found no constant difference between heat- and formol-killed preparations. We did not test vaccines made from very young cultures, but generally used eighteen-hour growths. The action of the vaccines was similar to that of the filtrates except that the vaccines were naturally more stable and more consistent in their effects. *E. coli* vaccine consistently gave as good protection as did vaccines of other species, and often better. We could show no better protection against the

TABLE III

EXPERIMENT 38.—MICE 18 TO 22 GM. EACH MOUSE, EXCEPT CONTROLS, RECEIVED 0.25 C.C. OF RABBIT ANTI-COLI VACCINE SERUM 26 HR. AND 3 HR. BEFORE INJECTION OF BACTERIA OR INTESTINAL CONTENTS.

DOSE OF VIRULENT E. COLI	SERUM-PROTECTED MICE	CONTROL, UNPROTECTED MICE
4 billion	Died	
1 billion	Lived	
100 million	Lived	Died
10 million		Died
1 million		Died
DOSE OF MOUSE INTESTINAL CONTENTS EMULSIFIED IN SALINE SOLUTION AND PIPETTED OFF	**SERUM-PROTECTED MICE**	**CONTROL, UNPROTECTED MICE**
20.0 c.c. concentrated	Died	
10.0 c.c. concentrated	Died	
2.0 c.c.	Died	Died
1.0 c.c.		Died
0.5 c.c.		Died
0.1 c.c.		Lived

Result: Protection by serum amounting to at least 1,000 minimal lethal doses against the virulent strain of *E. coli*, but less than 20 minimal lethal doses against the cloudy supernatant fluid from the intestinal contents.

homologous strains of *E. coli* than against heterologous. The degree of protection again in general rose with the virulence of the organism against which protection was aimed. Against emulsions of intestinal contents, or cultures of intestinal contents, the protection rarely exceeded ten minimal lethal doses, but against a relatively virulent strain of *E. coli* the protection reached into the thousands of minimal lethal doses.

5. *Protection by Substances Other Than the Above.*—We had by this time satisfied ourselves by experiments many times repeated that we knew how much protection could be obtained by injections of living organisms, filtrates, vaccines, and sera derived from the common intestinal organisms. In attempting to find a substance better than any of these, we entered upon a series of experiments in which we compared the protecting capacity of the derivatives just mentioned with the protection afforded by various other substances. In order to conduct comparative tests of this kind, it is most important to be sure that the protecting substances which are being compared are employed in the manner best suited to each. This means careful study of each new substance employed, to be certain that it is being correctly used. Obviously one cannot test all possible substances, or even test all possible ways of using one substance. As evidence for the statements we are about to make, we must point chiefly to the fact that we used over 7,000 animals in our various tests and attempted many variations in the use of our protecting agents in the hope that we would not overlook any manner of dosage that would give the best protection. In addition to the vaccines, sera, and filtrates of *E. coli*, enterococci, and *Cl. welchii*, we tested two brands of German commercial *E. coli* sera, *Staphylococcus aureus* vaccine, *E. coli* bacteriophage of our own production, amniotic fluid

concentrate, Bargen's *E. coli* and enterococcus vaccine, coli vaccine in gum tragacanth of our own make, Steinberg's bactragen, aleuronat, New York Board of Health typhoid vaccine, several pneumococcus vaccines, crude lecithin added to coli vaccine, broth, saline solution, acetic acid of varying strengths, aleuronat and starch mixture, sulfanilamide. We found several of these substances that gave as good protection as did coli vaccine but none that gave better in mice and guinea pigs.

NATURE OF THE PROTECTION OBTAINED

When any substance is injected into the peritoneal cavity, there is a reaction by the body which results in peritonitis. The degree of reaction varies with the nature and amount of the injected substance, and also with the reacting properties of the individual who receives the injection. It is not practical to inject enough of a bland substance like saline solution to produce a marked peritonitis. Therefore in order to obtain a strong peritoneal reaction, more irritating substances must be used. Shortly after the injection, the animal may show evidence of pain. There is an increase of peritoneal fluid. There may be within fifteen minutes a transient increase of small round cells in the peritoneal fluid, and shortly thereafter the large mononuclear cells, found in normal peritoneal fluid, are replaced by a great relative and actual increase of polymorphonuclear leucocytes. The only exception to this reaction that we found was when a large dose of virulent living organisms, such as *Cl. welchii,* was injected, in which case the animal often died without ever achieving a leucocytic response. Usually, however, as the leucocytes increase, the peritoneal fluid becomes thicker, clumps of fibrin appear containing cells and bacteria (if they have been injected), until, within about three or four hours, large, deeply staining mononuclear cells begin to appear in appreciable numbers, which we take to be young macrophages. By six hours after injection, the macrophages are clearly to be identified. Under favorable circumstances, phagocytosis is well under way by this time, both by leucocytes and macrophages. The proportion of macrophages continues to rise as degeneration of the various types of cells proceeds. At the end of five or six days, the peritoneal fluid may be hardly distinguishable from normal. Although the local peritoneal and subperitoneal phenomena are so pronounced that one is tempted to call the whole reaction local, it is obvious that the remainder of the body must also take part in it.

In general, the degree of immunity we obtained was highest when the peritoneal reaction was most intense. In fact, animals that were made so sick by the preliminary injection that they appeared about to die often withstood the largest doses of infecting organisms. Such intense peritoneal reactions could be produced by nonspecific substances like aleuronat and starch mixture, or by bacterial products like *E. coli* vaccine, and the protection afforded by each was in general the same. We therefore look on this protection as a function of the intensity of

the peritoneal reaction, short of actually causing the death of the animal, and also as a nonspecific phenomenon, whose efficacy against any infecting organisms is independent of the substance used to produce it. An exception to this statement is the protection afforded by *E. coli* bacteriophage, which was effective against its own homologous strain of *E. coli,* but ineffective against other strains of coli or against other organisms. The protection obtained by drugs may also be of a different nature.

Experiment 176 (Table IV) supports the idea of nonspecificity, because if the protection were specific, one would expect the homologous vaccine in each of the two series to protect better than the heterologous. This was not the case.

TABLE IV

EXPERIMENT 176.—MICE 18 TO 22 GM. TWO SETS OF MICE RECEIVED 50 MILLION E. COLI VACCINE INTRAPERITONEALLY 24 HR. BEFORE INJECTION OF LIVING BACTERIA. TWO OTHER SETS OF MICE RECEIVED 500 MILLION VACCINE MADE FROM STRAIN OF HEMOLYTIC STREPTOCOCCI OF RELATIVELY LOW VIRULENCE, AT SAME TIME. ONE OF EACH SET RECEIVED HOMOLOGOUS COLON ORGANISMS, AND ONE HOMOLOGOUS STREPTOCOCCI.

DOSE OF ORGANISMS	COLI VACCINE VS. COLI ORGANISMS	STREPTOCOCCUS VACCINE VS. COLI ORGANISMS	COLI VACCINE VS. STREPTOCOCCUS ORGANISMS	STREPTOCOCCUS VACCINE VS. STREPTOCOCCUS ORGANISMS
400 million	Died	Died	Died	Died
400 million	Died	Died	Died	Died
250 million	Died	Died	Died	Died
250 million	Died	Died	Died	Died
100 million	Died	Died	Died	Died
100 million	Died	Died	Lived	Died
50 million	Died	Died	Lived	Lived
50 million	Lived	Lived	Lived	Lived
10 million	Lived	Lived	Lived	Lived
10 million	Lived	Lived	Lived	Lived

DOSE OF ORGANISMS	UNPROTECTED CONTROLS VS. COLI	UNPROTECTED CONTROLS VS. STREPTOCOCCI
10 million	Died	Died
10 million	Died	Died
1 million	Died	Died
1 million	Died	Lived
100 thousand	Died	Lived
100 thousand	Died	Lived

Result: The vaccines in each case protected almost equally well against the heterologous organism as they did against the homologous strain. The fact that the colon strain was more virulent than the streptococci does not alter this conclusion.

SUMMARY OF THE EXPERIMENTS WITH MICE AND GUINEA PIGS

1. Any substance injected into the peritoneal cavity of mice or guinea pigs produces a peritoneal reaction.

2. If the reaction is severe enough, it is accompanied by a measurable degree of immunity against subsequent intraperitoneal injection of various organisms.

3. The immunity appears to be nonspecific, except in the case of certain substances like bacteriophage in which the protection afforded appears to be due chiefly to its specific bactericidal property.

4. The degree of immunity obtained may reach several thousand minimal lethal doses against relatively virulent organisms, such as strains of *E. coli* whose virulence has been artificially raised. *E. coli*, enterococci, *Cl. welchii*, and other intestinal organisms, as obtained from the intestinal tract or from pus, are in our experience always of low virulence, and against these strains the degree of immunity is usually of the order of ten minimal lethal doses. This is true also of intestinal contents, filtered through cotton.

5. We found no single protecting agent that was of outstanding value.

EXPERIMENTS WITH DOGS

We used mice and guinea pigs for the preliminary work just described, because many of the experiments required the use of fifty or more animals the same day. This part of the work was open to two obvious criticisms: first, that the method of producing peritonitis, i.e., by injection of a single dose of organisms, was unlike the method in which it usually arises in human beings, and, secondly, that the nature of the reaction in these small animals makes them unsuitable for experiments that could be interpreted in terms of human beings. We shifted to dogs, not only because of their greater size, but because we could produce in them a lesion that was not unlike acute gangrenous perforated appendicitis with subsequent diffuse peritonitis. The procedure was as follows: The dogs were anesthetized with sodium nembutal given intravenously. After preparing the skin of the abdomen we entered the peritoneal cavity through a right rectus incision a little above and to the right of the umbilicus. The appendix (or cecal appendage) was delivered into the wound, and the blood supply to the distal 4 cm. divided and ligated. A piece of umbilical tape was tied tightly around the appendix just proximal to the distal 4 cm., so as to shut off gross fecal leakage and to make sure that no blood supply reached the tip through the wall of the appendix. The distal 4 cm. was then laid open for its entire length, and the underlying mucosa wiped grossly clean of worms and feces, leaving behind, of course, many organisms on the mucosal surface. A T-tube was then placed into the midportion of the small intestine for enteral administration of drugs, and brought out through a close-fitting separate tract that was carried through subcutaneous tissues for several inches in order to prevent leakage of peritoneal fluid around the tube. The rectus wound was then carefully closed in layers. In spite of all efforts to produce a uniform lesion in this manner, it was of course impossible to do so because of inevitable variation in the nature and number of organisms present in the dogs' appendices. However, the lesion produced was uniform to this degree, that gangrene of the distal 4 cm. of the appendix always resulted, and

a generalized, not merely diffuse, peritonitis was present in all dogs that we autopsied in the acute stage. The appendix tip itself usually became a swollen, dark red, gangrenous mass. The peritoneal fluid was usually at first intensely bloody and present in large amounts. Each culture made from it grew *E. coli*, enterococci, and *Cl. welchii* and at least three other strains of variable nature. The peritonitis was therefore the result of a mixed infection. The control dogs, and those inadequately protected, usually died within forty-eight hours although there were some that died later, and an occasional survivor. The after-treatment consisted of morphine as indicated for pain, water to drink and food later if the dog survived long enough. In addition, the specific treatment being tested was given. When drugs were injected through the T-tube in water, an equal quantity of water was given by the same route to the controls. This never exceeded 150 c.c. in twenty-four hours.

Almost all of the survivors were autopsied three to five weeks after operation. Those sacrificed early showed a well-isolated abscess containing the tape that was used to tie off the appendix tip. After four or five weeks even this had often disappeared. The remainder of the peritoneal cavity showed little evidence of the severe infection which it had suffered.

The results of the experiments were as follows:

Controls.—No peritoneal protection, and no drugs except morphine for pain. Died in one day, 6; in two days, 4; in three days, 2; in four days, 1; in seven days, 1; survived, 2. Total: 14 died, 2 survived. Percentage of survivors, 12.5 per cent.

Bactragen.—One ampule, 30 c.c., given intraperitoneally twenty-four hours before operation. Treatment otherwise as for controls. This substance was selected as representative of the group that had been most effective in producing immunity in the guinea pig and mice experiments. It has furthermore been used extensively in dog experiments by Steinberg, and its best method of employment therefore probably ascertained. All the dogs which received it developed large amounts of bloody peritoneal exudate before operation. Died in one day, 1; died in two days, 2; died in three days, 4; died in four days, 1; died in five days, 1; died in eight days, 1; survived, 1. Total: 10 died, 1 survived. Percentage of survivors, 9 per cent.

In addition to the 11 dogs listed above were 2 which disrupted their wounds when they seemed extremely ill, discharged large amounts of pus, and finally recovered. This introduced a factor which makes it unfair to consider them in the series. There were also 2 other dogs which died, 1 under the anesthetic (which no uninjured dog in our experience of several hundred dogs has done), and 1 which was too sick the morning after receiving bactragen to operate upon. The last 2 provide evidence that the injection of bactragen is not without risk to the recipient.

Sulfathiazole.—Various methods of administration were tried, but the only one that we found practical in the dogs was the injection of a watery emulsion directly into the small intestine by T-tube. In this way they could not vomit it. They appeared to absorb it at variable rates. We tried sodium sulfathiazole both enterally and by vein, but found that this form of the drug was rapidly absorbed, giving very high blood levels, which soon fell sharply so that a continuous effect was not obtained. We finally came to giving two 5 Gm. doses the day of operation, one immediately and one six hours after operation, and two or three similar doses on subsequent days, depending on the apparent need for it. We seldom continued the drug for more than three days. The blood levels we obtained ranged from 0.5 mg. per cent to 8 mg. per cent, but were usually under 4 mg. per cent. Died in three days, 1; survived, 11. Percentage of survivors, 91.7 per cent.

There were three other dogs which received sulfathiazole while we were experimenting with the dosage and the route of administration of the drug, before we hit upon the T-tube method. Two received the drug in part by mouth and vomited an unknown quantity of it. One of these showed a blood level of zero after receiving 9 Gm. in twenty-four hours. The other showed a blood level of 9 mg. per cent the day of operation, but thereafter received only sodium sulfathiazole by rectum, subcutaneously, and intraperitoneally. These two dogs died in three and two days, respectively. The third dog received chiefly sodium sulfathiazole by T-tube, achieving variable blood levels up to 25 mg. per cent. The drug was stopped on the fourth day as he seemed nearly well, but he failed again after the tenth day and was sacrificed on the thirteenth day. He was found at autopsy to have diffuse peritonitis. As none of these three dogs received the drug in what we later found to be the correct method, we are reporting them separately, only for the sake of completeness. Were they included in the series, the survival rate would be 73 per cent.

Sulfathiazole Intraperitoneally.—We gave 5 dogs 10 Gm. of sulfathiazole powder intraperitoneally at the end of the operation, and 1 dog 12 Gm. This amount of powder was placed on and about the tip of the appendix after the usual lesion had been produced and the abdominal wound was ready to be closed.

Died in one day, 4; died in eight days, 1; survived, 1. Total: Died, 5; survived, 1. Percentage of survivors, 16.7 per cent.

Sulfapyridine.—This was administered by T-tube into the intestine in the same manner and amount as was the sulfathiazole. The blood levels were about the same.

Died in two days, 3; survived, 5. Percentage of survivors, 62.5 per cent.

One of the 3 that died had extensive pneumonia and perhaps should not be counted in the series. In addition, there were six other dogs that received the drug by mouth or by vein before the T-tube method

of administration was devised. Two of these survived, 2 died with minimal peritonitis but with pneumonia at fifteen days and nineteen days after operation, and 2 died clearly of peritonitis two days after operation.

Sulfanilamide.—This was similarly administered by T-tube, except that the doses given were 3.6 Gm. or sometimes 2.4 Gm. The blood levels ran from 9 to 20 mg. per cent.

One died in four days, 1 died in ten days, 2 survived. Percentage of survivors, 50 per cent.

In addition, there were 3 dogs which received the drug by mouth which died in two days, six days, and nine days. It may be that further tests would have shown that this drug was as good as sulfathiazole, but the results so far as we went, even though the sulfanilamide blood levels were higher, were not encouraging.

Sulfanilamide Intraperitoneally.—One dog received 6 Gm. about the appendix tip at the close of the operation, 5 received 9 Gm., 1 received 12 Gm., and 1 15 Gm. The blood levels of the dogs receiving 9 Gm. were 8, 16, 24, 34, 36 mg. per cent the morning after operation. By the following morning they had fallen to 1, 5, 4, 14, 20, respectively. Of the five dogs which received 9 Gm., 4 died of peritonitis (2 in three days, 1 in eleven days, 1 in seventeen days). One survived. The dog which received 6 Gm. survived; those which received 12 and 15 Gm. died in two days and three days.

Total: 6 died, 2 survived. Percentage of survival, 25 per cent.

The sulfanilamide intraperitoneally was apparently more beneficial than the sulfathiazole intraperitoneally, though not as effective as either when given and maintained by enteral administration. The appendix in this group of dogs did not become the large soft dark red mass that it did in most of the others. It turned into a relatively dry gray gangrene, nor was the peritoneal fluid as offensive.

E. coli Vaccine.—Given intraperitoneally the day before operation. It produced a sterile bloody peritoneal fluid, which on smear was hardly to be distinguished from that produced by bactragen, but was distinctly less in amount. One dog received 500 billion and died as a result of the anesthetic (cf. Bactragen), 1 received 250 billion which killed him without operation, 1 received 200 billion and died four days after the operation, 1 received 100 billion and survived. Four others received 100 billion total in two doses given twenty-four and four hours before operation plus 15 c.c. of *E. coli* bacteriophage total in the two doses. One of these died as a result of the injection. The others died within two days of operation.

Total: Died, 7; survived, 1. Survival percentage, 12.5 per cent.

E. coli Bacteriophage.—Two dogs received 10 c.c. of bacteriophage intraperitoneally at the end of operation and 5 c.c. intravenously the next morning. Both were dead in two days.

SUMMARY OF EXPERIMENTS WITH DOGS

1. Acute gangrenous perforated appendicitis was produced in dogs, which resulted apparently uniformly in generalized peritonitis.

2. Eighty-seven and one-half per cent of the untreated controls died of peritonitis.

3. Preoperative peritoneal protection afforded by bactragen, *E. coli* vaccine or *E. coli* bacteriophage did not lower the mortality or significantly prolong life.

4. Sulfathiazole placed in the peritoneal cavity in the vicinity of the appendix was of little apparent benefit; sulfanilamide similarly used seemed to have some value in lowering the mortality and in prolonging life.

5. Enteral administration of sulfapyridine, sulfathiazole and, less definitely, of sulfanilamide, was followed by a striking lowering of mortality. In the case of sulfathiazole, the mortality fell to 8.3 per cent, compared to 87.5 per cent for the controls. The mortality with sulfapyridine was 37.5 per cent, with sulfanilamide 50 per cent.

6. The peritonitis in each case cultured was found to be due to a mixture of organisms, among which the varieties commonly found in human peritonitis were predominant; viz., *E. coli*, enterococci, *Cl. welchii*. These results are summarized in Table V.

TABLE V

	TOTAL NO. DOGS	DIED 1 DAY	DIED 2 DAYS	DIED 3 DAYS	DIED 4 DAYS	DIED 5-7 DAYS	DIED 8-14 DAYS	DIED 15-21 DAYS	SURVIVED	DIED	SURVIVED %
Controls	16	6	4	2	1	1			2	14	12.5
Bactragen*	11	1	2	4	1	1	1		1	10	9
Sulfathiazole† (enterally)	12			1					11	1	91.7
Sulfathiazole (intraperitoneally)	6	4					1		1	5	16.7
Sulfapyridine‡	8		3						5	3	62.5
Sulfanilamide§	4				1		1		2	2	50
Sulfanilamide (intraperitoneally)	8		1	3			1	1	2	6	25
E. coli vaccine	8	3	3		1				1	7	12.5
Bacteriophage	2		2						0	2	0

*Two others disrupted wounds, discharged pus and survived; 1 other died from anesthetic; 1 other too sick following bactragen to operate upon.

†Three others received sulfathiazole inadequately. They were the first 3 to receive it, before the proper dose was established. All died; see text.

‡Two other dogs received sulfapyridine by mouth; these survived. Four other dogs received sulfapyridine by vein; 2 of these died on the second day, 2 died on the fifteenth and nineteenth days of pneumonia.

§Three others received drug by mouth; drug not retained. One survived, 2 died on the sixth and ninth days.

DISCUSSION

In the experiments with mice and guinea pigs we attempted to render the peritoneal cavity immune to infection by the organisms that com-

monly cause peritonitis in man. We found that several substances injected intraperitoneally twenty-four hours before the organisms would afford a limited immunity. We then took what seemed to be the best of these substances and compared their effect upon peritonitis in dogs with the effect of some of the sulfonamide drugs. The lesion produced in the dogs resembled that encountered in human beings, in that it was a peritonitis caused by a mixed growth of intestinal organisms emanating from a focus of gangrenous cecal appendage. It is significant that preoperative immunization of the peritoneum had little effect upon this type of lesion. Whereas we cannot express the degree of effectiveness of the sulfonamides in terms of minimal lethal doses, we believe our experiments justify their further trial as preventive and curative agents for peritonitis in man. If there is any advantage in intraperitoneal use of the crystals of these drugs, as opposed to administration by other routes, we failed to demonstrate it. The evidence is rather to the contrary. However, the number of dogs used was not sufficient to show conclusively which route of administration, or even which of the sulfonamide drugs, should be employed in human beings. These problems, we believe, should be solved by trial clinically.

We believe our experiments have shown that there is strong evidence that the sulfonamide drugs, properly selected and administered, will be of use in lowering the death rate from peritonitis. There was also some evidence of benefit from preoperative injection of substances into the peritoneal cavity in the effort to produce peritoneal immunity, but the benefit was slight and definitely less than that afforded by the sulfonamide drugs. There appears to be no benefit to be derived from preoperative injection that cannot be better obtained from the sulfonamides.

CONCLUSIONS

1. Various substances injected into the peritoneal cavity of mice or guinea pigs will produce an immunity to peritonitis caused by subsequent intraperitoneal injection of intestinal organisms.

2. The immunity appears to be nonspecific in nature.

3. The degree of immunity against organisms as obtained from the intestinal tract or from pus in the peritoneal cavity is usually of the order of ten minimal lethal doses. Only against strains of *E. coli*, whose virulence had been artificially enhanced, did the immunity rise to the order of 1,000 minimal lethal doses.

4. In experiments involving over 7,000 animals, no protecting substance of unique value was found. The best protecting agents were the irritative ones, such as the vaccines, potent sera, bactragen, or aleuronat and starch mixture.

5. In dogs with generalized peritonitis following artificially produced acute gangrenous perforated appendicitis, the immunity afforded by preoperative intraperitoneal injections of the best of the protecting agents was not sufficient to lower the mortality.

6. In a parallel series of dogs, however, postoperative enteral administration of the sulfonamide drugs, especially sulfathiazole, was followed by a striking lowering of mortality. Intraperitoneal use of these drugs was less effective.

7. On the basis of this evidence we recommend the use of the sulfonamides clinically but do not recommend the use of preoperative injections.

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EXUDATIVE INTERSTITIAL NEPHRITIS (PYELONEPHRITIS)

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INFLAMMATIONS of the interstitial tissues of the kidneys are commonly called pyelonephritis since in the majority of instances both the pelvis and the renal parenchyma are involved. But pyelonephritis is not always an accurate descriptive term since cortical abscesses occur not infrequently without involvement of the pelvis and a mild pyelitis may exist without notable extension into the parenchyma; these conditions may be designated cortical abscesses and pyelitis, respectively.

One objection to the use of the term interstitial nephritis is that this name was formerly applied to the contracted kidneys of chronic glomerulonephritis and primary hypertension because of the secondary condensation of connective tissue about the atrophic tubules. However, the older terminology has been in disuse so long that there will probably be no confusion from the use of this accurately descriptive term.

The most important feature of this group of renal diseases is that they are caused by the lodgement of bacteria in the kidneys. Glomerulonephritis and some of the tubular diseases are caused by toxic substances of bacterial origin, but in exudative interstitial nephritis the bacterial bodies lodge in the kidneys and provoke an inflammatory reaction. The causative organisms may be recovered from the kidney by cultural methods.

A. CORTICAL ABSCESS

Cortical abscesses often extend into the pelvis and may then be appropriately called pyelonephritis. Three anatomical types of cortical suppuration may be distinguished; viz., multiple small abscesses, carbuncle, and perinephric abscess.

1. *Multiple small abscesses* are chiefly of anatomical interest since they are usually found in autopsy material in association with staphylococcic bacteriemia, and there may have been no direct clinical evidence of their presence. In patients dead of staphylococcic bacteriemia it is not uncommon to find multiple small cortical abscesses which have not yet extended to the pelvis. The abscesses vary from microscopic dimensions to a diameter of 1 cm. or more. In sections of such kidneys it may often be determined that the abscesses begin in glomeruli and then extend into the adjacent tubular areas. The bacteria evidently lodge in the glomerular capillaries where they are attacked by polymorphonuclear leucocytes. In the early stages numerous leucocytes pass through the glomerular capillaries and are carried through the

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tubules toward the pelvis. The tubules associated with infected glomeruli are filled with polymorphonuclear leucocytes. It is probable that bacteria are carried in this way through the tubules to the renal pelvis. When the tubule becomes plugged with leucocytes, the infection spreads beyond its lumen into the adjacent tissue. This is the reason we so often see streaks of suppuration extending radially from the apex of the pyramid to the cortex.

A microscopic section through a small abscess shows a central mass of cocci surrounded by a zone of necrosis beyond which is a dense wide zone of polymorphonuclear leucocytes. The central necrosis is caused by the necrotizing toxin liberated by the staphylococci. In abscesses of subacute or chronic course the polymorphonuclear cells may be replaced partly or entirely by macrophages or lymphocytes.

As stated above, multiple small abscesses are found most frequently in cases of frank staphylococcic bacteriemia, but they are also frequent in those dead of diabetic coma and are seen occasionally in other diseases in which there was no clinical evidence of renal disease. Apparently these abscesses are caused by *Bacillus coli* and staphylococci and the infection evidently reaches the kidney through the blood stream.

Although no direct evidence is available, it is highly probable that small abscesses may heal leaving as residues only small scars or lymphocytic infiltrations.

2. *Renal Carbuncle.*—Carbuncle refers to a large multilocular honeycombed abscess. Good descriptions have been given by Brady, O'Conor, and Patch. The lesion is much more often unilateral than bilateral. The patient exhibits symptoms of a septic infection with localizing signs in the region of the involved kidney, but there is commonly no pyuria.

Usually an obvious source is demonstrable, a carbuncle, furuncle, or cellulitis of the skin. A few cases follow sore throat. Staphylococci are found in the carbuncle. The infection may break through the renal capsule to form a perinephric abscess.

Brady, who collected ninety-five cases from the literature, recommends drainage rather than nephrectomy.

3. *Perinephric abscess* refers to suppuration about the kidney outside of its capsule. It is widely believed that perinephric abscesses always represent an extension of a cortical abscess through the renal capsule, but Vermooten maintains that they may develop outside the renal capsule and are not extensions of a cortical suppuration. The etiology is the same as that of cortical abscess. Surgical drainage is usually recommended, especially when the kidney is not extensively destroyed.

B. PYELONEPHRITIS

The majority of infected kidneys show involvement of both the pelvis and the parenchyma and may be appropriately designated as pyelo-

nephritis. Pyelonephritis occurs both with and without obstruction of the urinary tract. If simple renal abscesses without pyelitis be excluded, the obstructive type is about twelve times as frequent as the nonobstructive but attracts less attention since the renal symptoms are overshadowed by the major illness responsible for the obstruction.

In our 32,360 autopsies there were 1,229 cases of hydronephrosis of varying degrees of intensity, and 60 per cent of these (744 cases) showed pyelonephritis. In Table I these cases are arranged with re-

TABLE I

BILATERAL AND UNILATERAL HYDRONEPHROSIS SHOWING FREQUENCY OF RENAL INFECTION IN DIFFERENT ETIOLOGICAL GROUPS

	NUMBER		BI-	UNI-	PER CENT
	MALES	FEMALES	LATERAL	LATERAL	INFECTED
Carcinoma of uterus		143	101	42	37.0
Pregnancy		60	30	30	23.0
Ureteral stricture	51	37	20	68	30.7
Urethral obstruction	37	3	34	6	72.0
Carcinoma of prostate	131		107	24	71.0
Hypertrophy of prostate	319		287	32	83.0
Carcinoma of bladder	76	16	69	23	82.0
Other obstructions of bladder	27	22	26	23	61.0
External ureteral obstructions	57	109	85	81	46.0
Paralytic, spinal cord	77	35	109	3	68.7
Paralytic, congenital	23	6	22	7	17.0
Total	798	431	890	339	60.0

spect to the cause of the hydronephrosis, and the percentage with pyelonephritis in each group. In the same autopsy material there were only 64 cases of pyelonephritis without hydronephrosis.

ROUTE OF INFECTION

1. *Ascending Infections.*—It will be noted in Table I that obstructive lesions of the urethra, bladder, and prostate produce infection of the kidneys about twice as frequently as obstruction of the ureters above the bladder. Obstructions which distend the bladder are almost invariably associated with cystitis, the ureteral orifices tend to become dilated and there is opportunity for reflux of infected urine into the ureters. These facts suggest that ascending infection plays an important role in the development of pyelonephritis resulting from obstruction of the lower urinary tract. On the other hand, when the block is in the ureter above the bladder, it is difficult to understand how ascending infection can occur.

Experimentally pyelonephritis may be produced in rabbits by introducing infection into the bladder and then obstructing the urethra; in dogs it may be produced without obstruction by infecting the bladder and cutting the ureteral orifices so that they remain open (Gruber and Rabinovitch).

In low urinary tract infections in man the ureters and the bladder form a common chamber, as the result of dilatation of the ureteral

orifices. Upon contraction of the bladder infected urine is forced into the ureters, and the bacteria may be transported to the pelvis of the kidney by mechanical dissemination through the urine, by to-and-fro movements, or by the motility of the organisms; e.g., colon bacilli.

When the infection reaches the renal pelvis, it produces pyelitis, and in the earlier stages a direct extension of the inflammation into the medullary pyramids may be seen. The infection may spread directly from the mucosa into the renal parenchyma or it may reach the parenchyma through minute tears of the mucosa which result from pelvic distention. In retrograde pyelograms it is sometimes noted that the radiopaque substance escapes into the peripelvic tissues (pyelointerstitial or pyelovenous reflux), and it is believed that this mechanism comes into play in obstructive hydronephrosis. In animals substances injected up the ureter under pressure pass directly into the veins (pyelovenous reflux), and the veins of the kidney may be readily injected through the ureter.

In the early stages ascending and hematogenous pyelonephritis may be distinguished by examination of the kidneys, but this distinction can seldom be made in the advanced stages.

2. *Hematogenous Infections.*—Pyelonephritis developing in the absence of urinary obstruction is generally believed to be of hematogenous origin. In the case of ureteral obstructions (Table I) the infection is also presumably hematogenous since none of the factors which favor ascending infection are present. It is possible that the infection reaches the kidney through the blood stream in some cases with low urinary obstruction. It is known that a positive blood culture may frequently be obtained after operations on the lower urinary tract, and even after catheterization (Scott, Young). The urethral chill is attributed to bacteriemia.

It is well established that hydronephrosis predisposes the kidney to hematogenous infection. If the ureter of one kidney of a rabbit be ligatured and staphylococci be injected intravenously after forty-eight hours, it will usually be found that multiple abscesses develop in the obstructed kidney but not in its normal mate. It is therefore easily possible that bacteria from the infected bladder enter the blood stream and thus reach the cortex of the hydronephrotic kidneys.

3. *Lymphogenous Infections.*—A few writers have supported the view that infection spreads from the bladder to the kidney through the periureteral lymphatics (Eisendrath, Sweet and Stewart). The chief evidence in support of this hypothesis is the presence of a lymphocytic exudate in the outer wall of the ureter. This finding is, however, more readily explained as a chronic ureteritis similar to a chronic pyelitis.

BACTERIOLOGY

Nearly all writers agree that colon bacilli are responsible for the great majority of infections of the urinary tract, the estimates varying

from 60 to 80 per cent (Cabot, Culver and co-workers, Haslinger, Hellström). The remainder are due chiefly to staphylococci. The authors have not distinguished obstructive and nonobstructive forms in their bacteriologic studies, and we therefore do not know the proportions of colon and staphylococcic infections in the two groups. However, it is clear that in the nonobstructive group, which comprises about 8 per cent of the pyelonephritides, the staphylococci are chiefly responsible since the infection usually originates in a known staphylococcic lesion such as a furuncle or carbuncle (Nesbit). Discrete cortical abscesses are due to staphylococci, but diffuse inflammations are more often caused by colon bacilli. Frequently a colon bacillus infection is superimposed on a staphylococcic inflammation.

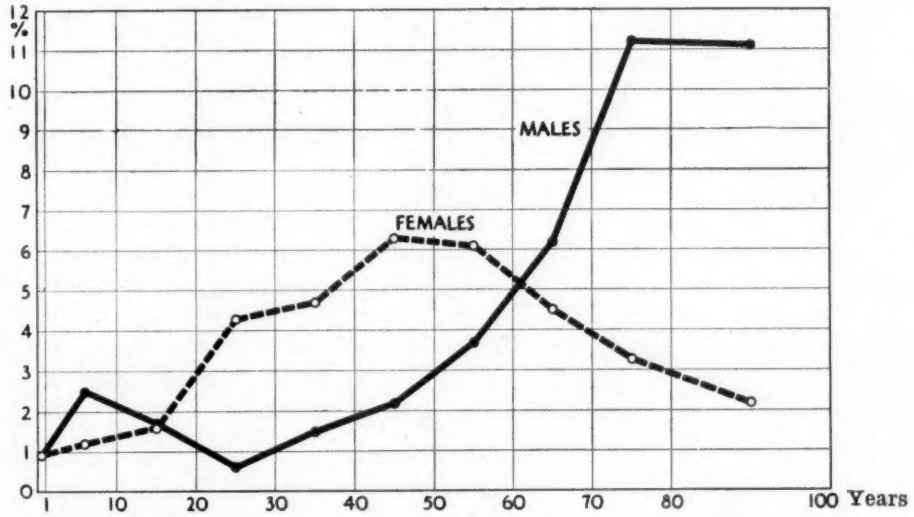

Fig. 1.—Distribution of hydronephrosis in autopsies according to age and sex.

A. OBSTRUCTIVE TYPE

Symptoms.—In pyelonephritis associated with obstruction the clinical picture is usually dominated by the disease responsible for the hydronephrosis such as hypertrophy of the prostate, carcinoma of the bladder, and carcinoma of the uterus, but evidences of infection (fever, leucocytosis, pain or tenderness in the region of the kidneys, etc.) may be superimposed on those of the major illness.

The age and sex distribution of the obstructive type of pyelonephritis corresponds to that of hydronephrosis (Fig. 1). During the third, fourth, fifth, and sixth decades it predominates in females because of pregnancy and carcinoma of the uterus, but after that time there is a great preponderance in males chiefly because of prostatic disease.

The pyelonephritis of pregnancy exhibits special features. Hydronephrosis of some degree is nearly always present during pregnancy and this predisposes the kidneys to hematogenous infection. About 1

per cent of pregnant women develop pyelitis. In McLane's ante-partum series of 98 cases, 60 developed pyelitis during the third trimester, 35 in the second, and 3 in the first. In 232 cases von Illyés found 145 on the right, 48 on the left, and 39 bilateral. Only a few patients give a history of pyelitis in childhood. The chief symptoms are chills, fever, leucocytosis, renal pain, and pyuria. By means of drainage and chemotherapy most of the patients may be cured before the onset of labor, but about 15 to 20 per cent of the cases result in abortion or premature delivery. The maternal mortality is about 3 per cent.

Pyelonephritis during the puerperal period is somewhat less frequent than during pregnancy and generally develops during the first week. Pyelonephritis occasionally recurs during a subsequent pregnancy, but there is no satisfactory evidence that it causes toxemia. Rarely the pyelonephritis of pregnancy continues as a chronic pyelonephritis, but we have no example of this in our collection.

In the paralytic and congenital types of hydronephrosis the associated pyelonephritis is easily recognized clinically. In all forms of hydronephrosis infection destroys more or less of the renal parenchyma and hastens the onset of uremia.

B. NONOBSTRUCTIVE TYPE

This form may be called hematogenous or descending pyelonephritis, and it is what clinicians usually have in mind when they speak of pyelonephritis. As pointed out above, however, the obstructive type is twelve times as frequent as the nonobstructive in autopsy material. There is usually no difficulty in distinguishing the two types at autopsy, but in chronic nonobstructive cases the shrinkage of the cortex may produce some enlargement of the pelvis and an associated inflammation of the ureter may cause a partial mechanical or paralytic obstruction.

1. *Acute Hematogenous Pyelonephritis.*—This lesion blends with cortical abscesses to such an extent that no sharp separation is possible. I have grouped under this heading only the cases in which cortical abscesses were associated with gross involvement of the renal pelvis and have classified all cases of less than four months' duration as acute. There are a large number of cases of cortical abscesses in our autopsies, but there are only 50 good examples of acute pyelonephritis.

The chief symptoms are fever, renal pain and tenderness, dysuria, tenesmus, pyuria, leucocytosis, and anemia. Weiss and Parker found the disease relatively common in early childhood, during pregnancy, and in old age. In children malformations in the urinary tract are a contributory cause, and in older subjects diabetes is often a predisposing influence. The prognosis is usually favorable.

Referring to the 50 fatal cases found in our autopsy records it is noteworthy that there was usually an associated disease, usually of infectious nature, which was largely responsible for death and over-

shadowed to some extent the symptoms referable to the kidneys. For convenience these 50 cases will be divided into four groups with respect to age.

(a) CHILDREN UNDER 1 YEAR OF AGE.—There are 7 cases in this group, 3 males and 4 females; the ages being 1 month, 2, 2, 3, 4, 7, and 9 months, respectively. Two patients had otitis media and meningitis, 1 had mastoiditis, 1 had pharyngitis, and 1 had an initial upper respiratory infection. In the 2 remaining cases there was no disease other than the pyelonephritis. The duration varied from ten to thirty days. The blood pressures were not recorded. At autopsy in each case both kidneys showed cortical abscesses with extensions into the pelves.

(b) CHILDREN FROM 1 TO 10 YEARS OLD.—There were 4 cases in this group, 3 females and 1 male, the ages being 2, 3, 6, and 8 years, respectively. The duration varied from one to three weeks. The complicating infections in 3 cases were acute osteomyelitis, meningococcic meningitis, and acute enterocolitis, respectively. In the fourth case there was a moderate unilateral hydronephrosis of undetermined cause which may have been the initial site of the infection. The blood pressures were not recorded. At autopsy the kidneys showed bilateral abscesses and suppurative pyelitis.

There is an extensive literature on acute pyelonephritis in children. Prior to 1909 it was generally regarded as a pyelitis on the assumption that the renal parenchyma was not involved. In 1909 Thomson and McDonald reported 25 cases, 21 girls and 4 boys, with 21 recoveries. In 2 autopsies on boys, aged 4 and 7 months, they found cortical suppuration as well as pyelitis. In 1910 Thiemich reported 7 autopsies, in 6 of which there was infection in the renal parenchyma.

Wieland, in 1918, described 45 cases with 4 deaths. There were 35 girls and 10 boys. In nursing infants the sexes were about equal, but all of his patients over 3 years old were girls. The predisposing causes were respiratory and intestinal infections, and *B. coli* was the organism usually found. Chown, in 1927, reported 21 autopsies on children under 2 years of age, all with parenchymal lesions in the kidneys. The sexes were about equal, and *B. coli* was the only organism found. Twelve of the 21 cases had infection outside the kidneys. The disease was bilateral in 12 instances, on the right in 6, and on the left in 2 cases.

It is now generally agreed that the pyelitis of children is pyelonephritis. In most instances it is secondary either to some obvious focus of infection elsewhere or to a respiratory or intestinal infection. The majority of the patients recover, but a few die and a few develop chronic pyelonephritis. Chronicity is favored by any anomaly which prevents drainage of the kidneys. With modern methods of treatment the percentage of recoveries should be notably increased and the duration of the illness shortened.

Wharton, Gray, and Guild made a careful study of 30 girls and young women from 3 to 14 years after acute pyelitis in childhood. One

had severe chronic pyelonephritis, and 16 others had slight but definite abnormalities in the urinary tract but no symptoms. One had a recurrence of pyelitis during pregnancy and another went through pregnancy without difficulty.

(c) Persons From 10 to 40 Years of Age.—There are 10 cases in this group, 8 females and 2 males, the ages being 17, 22, 23, 24, 27, 29, 29, 32, 34, and 34 years, respectively. The duration varied from two weeks to two months. The predisposing cause in 4 patients, 1 of whom was a boy 17 years old, was diabetes. In 1 patient the renal infection followed a peritonsillar abscess, and in another it was the outcome of puerperal endometritis. In 1 instance the disease followed an upper respiratory infection. Monocytic leucemia was the cause of 1 death in this group. Apart from the 4 cases of diabetes and the 1 of monocytic leucemia death was apparently due to uremia and this was established by the high blood urea nitrogen in 2 instances (urea nitrogen, 161, 173 mg. per cent). In 2 cases one kidney was removed shortly before death, but the infection continued in the other kidney and uremia developed. The disease was bilateral in each of the 10 cases.

Blood pressures were recorded in 6 of the 10 cases. In 4 patients the highest systolic pressure was 130 mm. Hg. In one the pressure was 148/96, but no kidney tissue was available for microscopic study. In another the pressure ranged from 100/64 to 150/90, and no renal arteriolosclerosis was found.

(d) Persons Over 40 Years of Age.—There are 29 cases in this group, 12 males and 17 females. Twenty-three were bilateral and 6 unilateral. The causes of death in the bilateral group were as follows: uremia, 8 cases; diabetes, 6 cases; and 1 each of pyemia, carcinoma of rectum, carcinoma of tongue, pernicious anemia, prostatic abscess, suppurative arthritis, cirrhosis of the liver, primary hypertension, and chronic glomerulonephritis. The duration of renal symptoms varied from two weeks to three and one-half months. The involvement of the kidneys was usually severe, but in only 9 cases was renal insufficiency the major cause of death, and 1 of these was complicated by chronic glomerulonephritis.

The blood pressures were recorded in 13 of the 29 cases. In 5 of the 13 cases the systolic pressure was 150 mm. Hg or higher, the lowest being 150/100 and the highest 180/90. Four of the 5 cases with hypertension had renal arteriolosclerosis. Therefore we need not believe that hypertension in acute pyelonephritis is due to the renal infection. Weiss and Parker found only 1 instance of hypertension in their patients with acute pyelonephritis.

2. *Chronic Hematogenous Pyelonephritis.*—Infections of more than four months' duration may be classified as chronic. In this discussion only the nonobstructive type is considered. The symptoms vary with the severity of the disease. Frequently there are acute exacerbations at irregular intervals during which the symptoms are more pronounced.

During exacerbations there are commonly fever, leucocytosis, renal tenderness or pain, nausea, pyuria, etc. In the intervals between acute attacks and in chronic forms of low intensity there may be only a low-grade fever, a loss of appetite or fatigability. Pyuria is found only during exacerbations.

The disease may persist for many years before death is brought about by uremia or infection.

In the literature "chronic pyelonephritis" is applied almost exclusively to contracted kidneys, but a marked shrinkage of the kidneys is not a necessary feature. When death results from an acute exacerbation of a chronic infection, the kidneys may be of increased size (Case 9, Table II).

TABLE II

BILATERAL CHRONIC PYELONEPHRITIS WITHOUT URINARY OBSTRUCTION

	AUTOPSY NO.	AGE (YR.)	SEX	DURATION	BLOOD UREA NITROGEN MG. %	BLOOD PRESSURE	WEIGHT OF HEART (GM.)	WEIGHT OF KIDNEYS (GM.)	HYALINE ARTERIOLES
1.	34-2178	8	F	6+ yr.	208	125/90	110	Very small	?
2.	25-304	20	M	2 yr.	236	100/55	307	R. 70 L. 60	?
3.	39-2543	25	M	13 yr. 10 mo.	200	152/94	425	R. 75 L. 43	Chronic glomerulonephritis
4.	37-2186	27	F	7 mo.	210	130/90	300	R. 100	?
5.	39-1371	30	F	20 mo.	N.P.N. 286	112/74 140/80	325	R. 74 L. 100	0
6.	36-1442	44	F	28 yr. 6 yr.	199	198/140	290	L. 100	3
7.	26-615	45	M	2+ yr.	86.2	152/88	280	280	0
8.	25-464	46	F	3 yr.	48	?	250	R. 520 L. 100	0
9.	30-1016	46	F	1 yr.	?	160/82	260	640	0
10.	40-1753	48	F	26 yr.	68	140/90 3 yr. 110/80 2 days	290	R. 100	?
11.	40-3851	48	F	14 yr.	N.P.N. 80	115/65	190	R. 40 L. 40	0
12.	36-1278	49	F	10 mo.	52	195/100	295	R. 290 L. 150	Acute thromboarteritis
13.	28-1642	48	M	9 yr.	145	?	350	R. 60 L. 150	0
14.	19-224	59	M	2 yr. 8 mo.	P.S.P. 35	115/70	195	300	0

Both Staemmler and Pfeiffer found pyelonephritic contracted kidneys very common in autopsy material, and estimated that from one-fourth to one-third of contracted kidneys were of this type. From one-third to one-half of their cases were unilateral. But these estimates

must include types of disease which we have classified as hydronephrosis and unilateral dwarfed kidneys. In our 32,360 autopsies there are only 14 cases of chronic bilateral pyelonephritis of the nonobstructive type, and only 8 of these were typical bilateral contracted kidneys. The disease is more common in females than in males.

The macroscopic changes in the kidneys are characteristic and have been well described by Staemmler and Pfeiffer. The external surfaces show coarse sunken areas separated by islands of persistent cortex (Fig. 2, *1*). The sunken areas are regions of marked cortical atrophy, and the elevated areas are portions of intact cortex. The extent of the atrophy of course may be greater in unilateral than in bilateral disease. The thin cortices of the kidneys give an impression of hydronephrosis, although there is little or no enlargement of the pelves.

In the atrophic areas there is a dense lymphocytic infiltration especially marked in the medulla. The cortex corresponding with the infiltrated medulla may show some lymphocytic exudate but the principal change is atrophy. The first stage of the disease is a cortical inflammation with a spread of the cellular exudate from the cortex into the medullary pyramids. As a result of destruction of tubules the corresponding cortical segments undergo a slow disuse atrophy which results in the formation of large deep cortical depressions. The infiltrate usually has a patchy distribution leaving areas of normal parenchyma between the atrophic portions. The amount of persisting parenchyma in a pyelonephritic contracted kidney naturally depends upon the extent of the original inflammatory exudate.

In bilateral forms of pyelonephritis death occurs before atrophy has reached the extreme degree that is found in unilateral cases. The atrophic cortical areas are interspersed with normal tubules and glomeruli. The completely atrophied segments are composed almost entirely of hyaline glomeruli and atrophic tubules (Fig. 2, *2*).

In unilateral disease the atrophy may become extreme, and in such instances the thin cortex may consist only of hyaline glomeruli, small tubules filled with casts, and atrophic arteries (Fig. 2, *3*).

The arteries supplying the atrophic segments of the kidneys show thickened walls (Fig. 2, *3* and *4*) and this appearance has been mistaken for primary arterial disease (Weiss and Parker). But this vascular change is a disuse atrophy, an adjustment of the lumen of the vessel to its decreased blood flow. Microscopic examination of medium-sized arteries shows that the intimal thickening is due to reduplication of the internal elastic lamella. One would expect this to be a collagenous intimal thickening, as in the Jores type, but it is elastic tissue. It is independent of hypertension since it occurs in chronic pyelonephritis with normal blood pressure.

In disuse atrophy the small renal arteries and arterioles show thick walls chiefly the result of contraction. The internal elastic lamella is not reduplicated but shows very marked folding corresponding with

the decreased size of the lumen (Fig. 3, *5*). The most conspicuous alteration in these vessels is medial fibrosis, the smooth muscle being partly replaced by collagenous fibers. In chronic glomerulonephritis the afferent arterioles of hyaline glomeruli show small lumina and their walls have a semihyaline appearance (Fig. 3, *6*). With the azocarmine stain it is seen that this homogeneous appearance is due to medial fibrosis (Fig. 3, *7*). There is no intimal change. Occasionally in disuse atrophy the small arteries show collagenous intimal thickening.

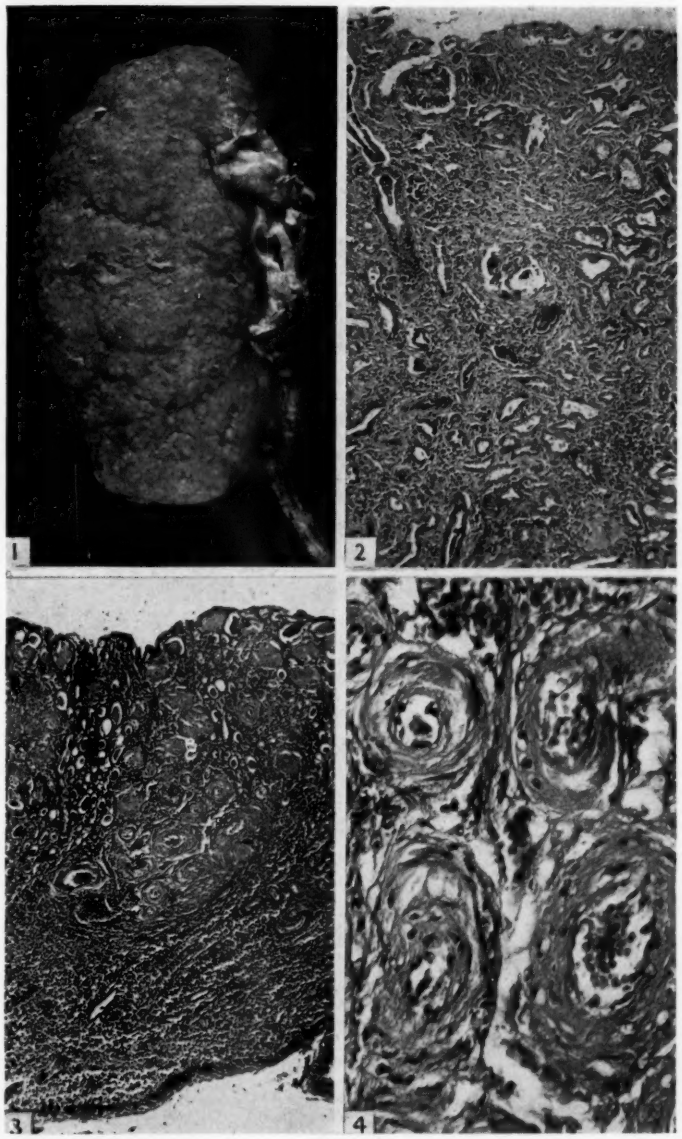

Fig. 2.—*1.* Case 11, Table II. Chronic hematogenous pyelonephritis. External surface of kidney. Photograph, natural size. *2.* Case 11, Table II. Segment of atrophic cortex in chronic pyelonephritis. Note the severe tubular atrophy. *3.* Unilateral hydronephrosis complicated by pyelonephritis. Note the extremely thin cortex, the inflammatory exudate near the pelvic epithelium, the hyaline glomeruli, the thick-walled arteries, and the small tubules filled by casts. *4.* Disuse atrophy of small arteries. Higher magnification of an area from *3*. The arteries show medial fibrosis.

Weiss and Parker described several cases of pyelonephritis with the vascular changes of malignant hypertension, but it is highly improbable that there is any causal connection between these two diseases.

BLOOD PRESSURE IN CHRONIC PYELONEPHRITIS

1. *Bilateral Pyelonephritis.*—Several writers have noted that bilateral pyelonephritis is occasionally accompanied by hypertension. Haslinger,

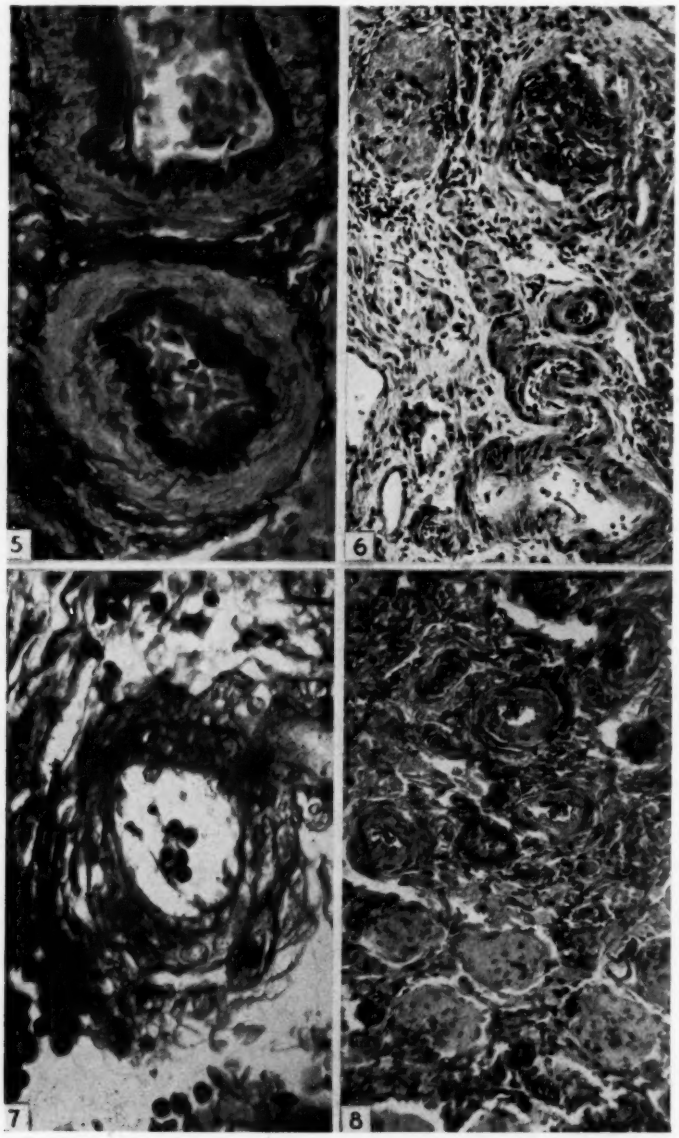

Fig. 3.—*5*. Case 11, Table II. Chronic pyelonephritis. Disuse atrophy of small arteries. Note the extreme folding of the internal elastic lamella due to shrinkage of the lumen. Orcein stain. *6*. Chronic glomerulonephritis. Disuse atrophy of afferent arteriole of a hyaline glomerulus. 7. Chronic glomerulonephritis. Disuse atrophy of afferent arteriole of a hyaline glomerulus, showing medial fibrosis. Azocarmine stain. 8. Kidney of a dog. Severe atrophy of kidney due to constriction of renal artery. The blood pressure was high for eighteen months but then returned to normal and remained so for one year before the experiment was terminated. Note hyaline glomeruli and almost complete disappearance of tubules.

1928, found no noteworthy increase of blood pressure, but Staemmler as well as Pfeiffer found the pressure elevated not infrequently. Weiss and Parker found hypertension in about 50 per cent of their patients, but these investigators have confused their records by the inclusion of several obvious cases of malignant hypertension.

Longcope, who is often quoted on this topic, stated that the blood pressure is seldom elevated during the early stages of the disease, but that hypertension was present in 10 of 15 advanced cases. But of the 10 cases with hypertension 5 had renal arteriolosclerosis and 1 had chronic glomerulonephritis.

Crabtree is not impressed with the frequency of hypertension in chronic pyelonephritis, since only 2 of 30 women with this disease under his observation had hypertension.

The blood pressure was recorded in 12 of our 14 cases of chronic bilateral pyelonephritis (Table II). Hypertension was present in 5 cases, but 1 of these (Case 3) also had chronic glomerulonephritis, and another had severe renal arteriolosclerosis (Case 6). In Case 12 there was a terminal acute thromboarteritis which was presumably responsible for the hypertension. The size of the hearts, as shown in Table II, is evidence that none of these patients had a prolonged severe elevation of blood pressure such as occurs in primary hypertension; the only instance of cardiac hypertrophy was in the case of chronic glomerulonephritis (Case 3).

It may therefore be said that moderate hypertension occurs occasionally in uncomplicated chronic bilateral pyelonephritis, but a severe prolonged hypertension with cardiac hypertrophy in this disease is usually due to a complicating lesion such as chronic glomerulonephritis or renal arteriolosclerosis.

An illustrative example of chronic bilateral pyelonephritis with contracted kidneys is as follows:

CASE 11 (Table II).—A married woman, 48 years of age, was first seen on March 26, 1940. She gave a history of an attack of "kidney trouble" fourteen years previously. Two years ago she had another attack characterized by heavy albuminuria. For the past six months she had complained of poor appetite and loss of weight. Her blood pressure on admission was 115/65 mm. Hg. There was heavy albuminuria and many pus cells were found in the urine. The two-hour excretion of phenolsulphonephthalein was 7 per cent. Nonprotein nitrogen was 60 mg. per cent. There was a normochromic anemia with 2,700,000 erythrocytes and 10.6 Gm. of hemoglobin. The temperature was 99° F. On May 19, 1940, the nonprotein nitrogen was 80 mg. per cent. Death occurred May 28, 1940.

Autopsy.—There was no edema. The heart weighed 190 Gm. Fatty metamorphosis of the liver was present. Each kidney weighed 40 Gm. and showed granular surfaces and thin cortices. The pelves and ureters appeared normal.

Microscopic study of the kidneys showed a heavy lymphocytic infiltration, especially marked in the medullary and deep cortical areas. There was widespread tubular atrophy and most of the glomeruli were hyaline (Fig. 2, *2*). There were small islands of normal glomeruli and tubules. The arteries showed the changes characteristic of disuse atrophy. There was no hyaline arteriolosclerosis.

A case illustrating a complication with chronic glomerulonephritis is as follows:

CASE 3 (Table II).—A male, 25 years old, known to have had albuminuria at the age of 12 years and nocturia for many years. He has had poor health for the past eighteen months and definite renal disease was recognized fourteen months before death. Upon admission, eleven days prior to his death, he was drowsy and had a uremic odor on his breath. The blood pressure was 157/88 and 152/94. Hemoglobin, 58 per cent; erythrocytes, 2,500,000; leucocytes, 10,800. Albumin, ++; specific gravity of urine, 1012. During a ten-day period with an average fluid intake of 2,320 c.c. the average amount of urine daily was 946 c.c. Blood urea nitrogen, 200 mg. per cent; creatinine, 21.7 mg. per cent.

At autopsy there was a slight dependent edema. The heart weighed 425 Gm. and showed left ventricular hypertrophy and moderate coronary atherosclerosis. The right kidney weighed 75 Gm. and the left 43 Gm. The pelves and right ureter were dilated, but the left ureter was of normal size. There was no obstruction in the urinary tract. The cortices of both kidneys were markedly atrophic and the external surfaces were covered with coarse depressions.

Microscopically the kidneys showed a heavy lymphocytic infiltration especially in the medullary portions. There were small scattered areas of persistent normal glomeruli and tubules but the great majority of the tubules were very atrophic and their glomeruli were hyaline. Many of the hyaline glomeruli showed evidence of an old proliferative glomerulonephritis, but the greater part of the atrophy was attributable to the heavy lymphocytic infiltration. The arteries and arterioles showed no changes except a moderate disuse atrophy.

The interpretation was that of a chronic pyelonephritis associated with chronic glomerulonephritis.

2. *Unilateral Pyelonephritis.*—In our autopsy records there are 94 cases of unilateral dwarfed kidney, but aside from 8 cases of true hypoplasia and 14 examples of unilateral polycystic disease it is usually impossible to determine the cause of the atrophy with certainty. In a few cases there was a lymphocytic exudate suggesting pyelonephritis, but in the vast majority there was no evidence of inflammation. With the exception of the cases of true hypoplasia and cystic disease the only change was atrophy, and the thick-walled arteries were evidence that the kidney originally had been much larger. In some instances it appeared that hydronephrosis was responsible for the atrophy and in other cases atherosclerosis of the large arteries was suggested.

None of the 94 cases was a "surgical" kidney in the sense that it was producing local symptoms. In the great majority the atrophy was so extreme that little or no functioning parenchyma remained.

Recently the chief interest in unilateral pyelonephritis has centered about its supposed relation to hypertension. Several cases have been reported in which a previously high blood pressure returned to normal after removal of the diseased kidney. At first it was only atrophic pyelonephritis that was supposed to cause hypertension, but now many urologists believe that any type of low-functioning or nonfunctioning

kidney may produce high blood pressure. Mulholland expressed the extreme view that all cases of hypertension should be studied urologically.

The theoretical argument for nephrectomy in hypertension with unilateral renal disease is based upon Goldblatt's experiments on dogs in which he showed that constriction of one renal artery usually causes moderate hypertension. The hypertension produced in this way is, however, not severe and does not persist permanently as it does when both renal arteries are constricted. It is believed that the ischemic kidney secretes renin which causes elevation of blood pressure. A very important feature of this experiment, frequently overlooked, is the fact that if the constriction of the artery is severe enough to produce atrophy of the kidney, the blood pressure will return to normal after the atrophy is well advanced. In the experiment which Pedersen and I performed, viz., obstruction of one renal vein, the blood pressure returned to normal after two months and it was found that the obstructed kidney was markedly atrophic. In 2 dogs with bilateral constriction of the renal arteries, which I have studied, the blood pressure was high for over eighteen months but then fell to normal levels and remained so for about one year before the animals were killed. At autopsy in each case one kidney had developed a collateral circulation and was normal while the other showed extreme atrophy. There is extensive lymphocytic infiltration and the only persistent parenchyma is represented by groups of small tubules filled with casts (Fig. 3, *8*). These atrophic kidneys in the dogs were evidently incapable of producing renin, and it may therefore be argued that human atrophic kidneys with minimum amounts of parenchyma are likewise incapable of producing renin. There is no feature of the Goldblatt experiment which justifies the removal of a completely atrophic human kidney.

The literature concerning the effect of nephrectomy on hypertension is summarized in Table III. Twenty-five cases are recorded in which a small kidney with little or no function was removed in the hope that a fall of blood pressure would result. Cases 2, 13, 15, and 16 cannot be considered cured since the duration of the postoperative period of normal blood pressure was not given. Similarly Cases 5, 6, and 14 must be omitted from consideration since the period of observation was too short. It is well known that nonspecific operations such as hysterectomy often cause hypertension to subside for several months. The former practice of extracting teeth as treatment for hypertension was based upon the observation that a temporary fall of blood pressure frequently resulted.

In Case 18 the evidence of hypertension is hardly satisfactory and in Case 19 the marked variation in the preoperative blood pressure throws doubt upon the result. There are only 5 cases (Cases 3, 10, 21, 23, and 24) in which the blood pressure fell to normal and remained so for one year or longer.

In Crabtree's cases (Cases 11 and 12) the blood pressure showed a postoperative fall but subsequently returned to a high level. Three cases have come under my personal observation: 2 females, aged 14 and 26 years, and 1 male 9 years old. Each had severe hypertension of long duration and one low-functioning small kidney that was producing no renal symptoms. In the 2 females the small kidneys showed

TABLE III

EFFECT OF NEPHRECTOMY ON HYPERTENSION WITH UNILATERAL RENAL DISEASE

AUTHOR	DATE	AGE	SEX	PREOPERATIVE BLOOD PRESSURE	POSTOPERATIVE BLOOD PRESSURE	INTERVAL	LESION
1. Boyd and Lewis	(1938)	31	M	180/100 200/120	124/84	6.5 mo.	Large infarct
2. Leadbetter and Burkland	(1938)	5	M	170/110 145/85	Normal	?	Ectopic kidney; muscle plug in artery
3. Nesbit and Ratliff	(1940)	37	M	180/110	Normal	1 yr.	Pyelonephritis
4. Nesbit and Ratliff	(1940)	35	M	200/110	140/80	10.5 mo.	Small, contracted
5. Nesbit and Ratliff	(1940)	58	M	205/110	150/110	2 wk.	?
6. Nesbit and Ratliff	(1940)	47	F	190/120	120/95	13 days	Pyelonephritis, hydronephrosis
7. Nesbit and Ratliff	(1940)	28	F	220/110 280/140	220/110	3 mo.	Pyelonephritis, arteriosclerosis
8. Nesbit and Ratliff	(1940)	40	F	200/120	200/125	?	25 Gm., arteriosclerotic
9. Nesbit and Ratliff	(1940)	24	M	170/100	130/64	5 mo.	Hydronephrosis
10. Barney and Suby	(1939)	10	F	185/130	98/60	21 mo.	Pyelonephritis
11. Crabtree	(1938)	14	M	250/170	130/? high	1 wk. 1 yr.	Hydronephrosis
12. Crabtree	(1938)	27	F	180/? 210/?	120/76 145/90 196/124	3 wk. 6 yr. 11 yr.	Pyelonephritis, glomerulonephritis
13. Crabtree	(1938)	40	M	160/120 130/?	low	?	?
14. Ratliff	(1939)	51	F	180/100	120/80	At discharge	Tuberculosis
15. Ratliff	(1939)	32	M	230/170	155/110	?	Arteriosclerosis
16. Quinby	(1923)	14	M	250/170	138/90	?	Hydronephrosis
17. McIntyre	(1939)	34	M	180/104	134/78	10 mo.	Pyelonephritis
18. Bothe	(1939)	7	F	130/85	110/65	4.5 yr.	Pyelonephritis
19. Butler	(1937)	7	M	122/90 168/110	115/75	20 mo.	Pyelonephritis
20. Butler	(1937)	10	F	190/120	92/70	3 mo.	Pyelonephritis
21. Barker and Walters	(1940)	42	M	170/120 200/140	130/90	2 yr.	Pyelonephritis
22. Barker and Walters	(1940)	46	M	170/110	115/85	6 mo.	Pyelonephritis
23. Barker and Walters	(1940)	34	F	180/115	122/92	1 yr.	Pyelonephritis
24. Barker and Walters	(1940)	52	F	186/110	125/85	1 yr.	Pyelonephritis
25. Barker and Walters	(1940)	7	F	205/150	110/77	3 mo.	Pyelonephritis

chronic pyelonephritis and arteriolosclerosis; in the male there were only arteriosclerosis and arteriolosclerosis. The kidneys contained only minimal amounts of functioning parenchyma. Nephrectomy had no favorable effect on the hypertension in these 3 cases; there was not even a temporary decrease.

In our 94 cases of unilateral dwarfed kidney there are 44 in which the blood pressure was recorded (Table IV). Twenty-eight of the 44

TABLE IV

UNILATERAL DWARFED KIDNEYS

SERIAL NO.	AUTOPSY NO.	AGE	SEX	WEIGHT OF RIGHT KIDNEY	WEIGHT OF LEFT KIDNEY	WEIGHT OF HEART	BLOOD PRESSURE	DISEASE
1.	36-1625	55	M	213	45	355	140/68	True hypoplasia
2.	37-781	65	M	60	250	400	116/92	True hypoplasia
3.	39-742	55	F	225	75	325	120/70	True hypoplasia
4.	32-548	60	M	250	95	380	160/94	Polycystic
5.	35-1887	62	F	42	107	650	220/136	Polycystic
6.	37-901	79	M	170	45	500	125/86	Polycystic
7.	28-1191	42	F	20	190	400	196/90	
8.	28-1446	29	F	70	10	430	114/74 194/124	
9.	29-675	74	M	270	60	?	145/75	
10.	30-976	77	M	30	220	360	200/105	
11.	30-1941	70	M	200	30	510	132/80	
12.	32-401	78	M	Normal	30	310	162/78	
13.	32-1983	87	F	150	40	320	104/56	
14.	34-1118	33	F	200	30	250	156/82	
15.	34-1301	65	F	16	209	440	180/110	
16.	34-1808	60	M	20	180	530	208/130	
17.	36-1090	36	F	240	20	400	142/90	
18.	37-184	55	M	230	65	460	174/120	
19.	37-571	33	M	190	30	700	256/160	
20.	37-1507	68	F	18	233	440	190/110	
21.	37-1800	57	F	145	35	590	170/110	
22.	37-1956	77	F	35	145	452	140/90	
23.	37-2157	13	F	15	70	190	210/150	Hypoplasia
24.	38-1779	66	M	Very small	260	300	112/90	Pyelonephritis
25.	39-311	87	M	50	185	500	110/60	
26.	39-793	74	M	190	10	?	225/132	
27.	15-293	66	F	150	18	?	180/ ?	
28.	29-1485	81	M	160	50	460	200/120	
29.	31-1737	64	M	193	44	520	230/140	
30.	33-1302	56	M	40	210	300	158/90	
31.	34-334	72	M	50	170	530	162/90	Arteriolosclerosis in both kidneys
32.	34-992	58	F	106	50	312	150/82	
33.	32-837	82	M	50	110	280	98/60	
34.	35-1675	81	F	150	35	520	178/80	
35.	35-2090	84	M	32	127	486	160/90	
36.	35-2102	55	F	59	183	450	146/90	
37.	36-177	16	M	115	30	375	172/116	
38.	36-856	51	F	40	110	520	236/120	
39.	36-1948	88	M	50	125	260	135/80	
40.	37-1046	69	M	175	27	605	220/120	Uremia
41.	37-2067	49	F	200	20	600	160/140	Uremia
42.	37-465	46	F	128	28	437	142/90	
43.	36-1066	60	M	150	37	334	145/95	
44.	36-1106	69	M	185	39	668	170/112	

(63 per cent) had hypertension. Of the 35 persons over 50 years of age, 67 per cent had hypertension. This is definitely higher than in Wetherby's dispensary patients (Table V), and it suggests a causal connection between unilateral dwarfed kidney and hypertension. But it is highly probable that hypertension with its associated vascular disease is responsible for the dwarfed kidney; i.e., that the dwarfed kidney is an effect and not a cause of hypertension. The few cases in which material from the large kidney was available showed hyaline arteriolosclerosis.

Interesting data on the relation of unilateral renal disease to hypertension are furnished by Pearman, Thompson, and Allen. These investigators found the incidence of hypertension in 500 cases of each of the following diseases as follows: pyelonephritis, 9 per cent; nephrolithiasis, 7 per cent; duodenal ulcer, 4 per cent; adenomatous goiter without hyperthyroidism, 10 per cent; disease of the gall bladder, 7 per cent. In 2,000 cases of hypertension the incidence of gall bladder disease was 4.4 per cent; adenomatous goiter, 2.5 per cent; duodenal ulcer, 1.3 per cent; and arthritis, 6.3 per cent. These data suggest that pyelonephritis, like adenomatous goiter and arthritis, is merely associated with hypertension and is not a causative factor.

The few cases of hypertension that appear to have been permanently relieved by unilateral nephrectomy may have been cases of acute hypertension.

Hydronephrosis shows no convincing relationship to hypertension. The frequency of hypertension with hydronephrosis in persons over 50 years of age is shown in Table V. It will be noted that there is no significant difference from Wetherby's control in dispensary patients. Very few of Wetherby's cases had any symptoms of hypertension. However, we have 2 cases of bilateral congenital hydronephrosis of long duration in which hypertension was a prominent feature.

TABLE V

HYPERTENSION IN HYDRONEPHROSIS; A COMPARISON WITH WETHERBY'S DISPENSARY PATIENTS

HYPERTENSION (150 MM. HG OR HIGHER) IN PERSONS OVER 50 YEARS OLD

	% MALES	% FEMALES
Wetherby (1,558 cases)	38	57.5
Hydronephrosis (present series) (481 cases)	46	52.0

SUMMARY

The obstructive form of pyelonephritis is about twelve times as frequent as the nonobstructive type in autopsy material. Its age and sex distribution corresponds with that of hydronephrosis, and the symptoms are usually overshadowed by those of the disease causing the hydronephrosis.

Infection of the kidneys is present at autopsy about twice as frequently (61 to 83 per cent) in those with low urinary tract obstruction as in those with ureteral obstruction above the bladder (23 to 46 per cent).

The incidence of chronic hypertension in hydronephrosis is not greater than in a control population of corresponding age, but we have two examples of severe chronic hypertension associated with congenital bilateral hydronephrosis of long standing.

Cortical abscesses are frequent in post-mortem material, but only 40 cases of typical acute nonobstructive pyelonephritis were found in over 32,000 autopsies.

There were only 14 examples of chronic bilateral nonobstructive pyelonephritis in our autopsies. The available evidence indicates that this disease seldom causes chronic hypertension.

Unilateral chronic atrophic pyelonephritis probably does not cause chronic hypertension, but reports have been published of 5 cases in which the blood pressure has remained normal for over one year after nephrectomy. There may be some other explanation for these successful cases since many failures have been observed.

In unilateral renal ischemia produced by Goldblatt's method the blood pressure returns to normal if the ischemic kidney becomes markedly atrophic.

The thick-walled arteries in atrophic pyelonephritis represent disuse atrophy and not primary vascular disease.

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OBSERVATIONS ON THE DISTRIBUTION AND TRANSPORT OF GAS IN THE GASTROINTESTINAL TRACT OF INFANTS AND YOUNG CHILDREN

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INTRODUCTION

INFORMATION obtained from the study of roentgenograms of the abdomen has come to play such an important role in the diagnosis and treatment of intestinal obstruction that it is necessary for all clinicians to have a clear understanding of certain normal variations

Fig. 1.—Roentgenogram of the abdomen of an 18-month-old child. Accumulations of gas are seen in the stomach, small bowel, and colon.

in the x-ray appearance of intestinal gas in children and infants. While it is generally recognized that adults exhibit normally no gas in the small bowel which can be seen on the x-ray film, experience teaches that this is not so in children. Furthermore, if the diagnosis of in-

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testinal obstruction due to congenital lesions is to be promptly recognized in newborn infants information as to the speed with which gas appears in the gastrointestinal tract and is transported through it should be available.

A few observations on these questions have already been recorded. Snow and Cassasa studied 50 newborn infants and found that whereas 25 of these exhibited unusually large amounts of gas in the small and large intestine when lying in the recumbent position, it largely disappeared in 22 of the infants after lying in a semi-inclined position for twenty-four hours. In their experience gas was found only rarely in the small intestine of infants over 3 months of age.

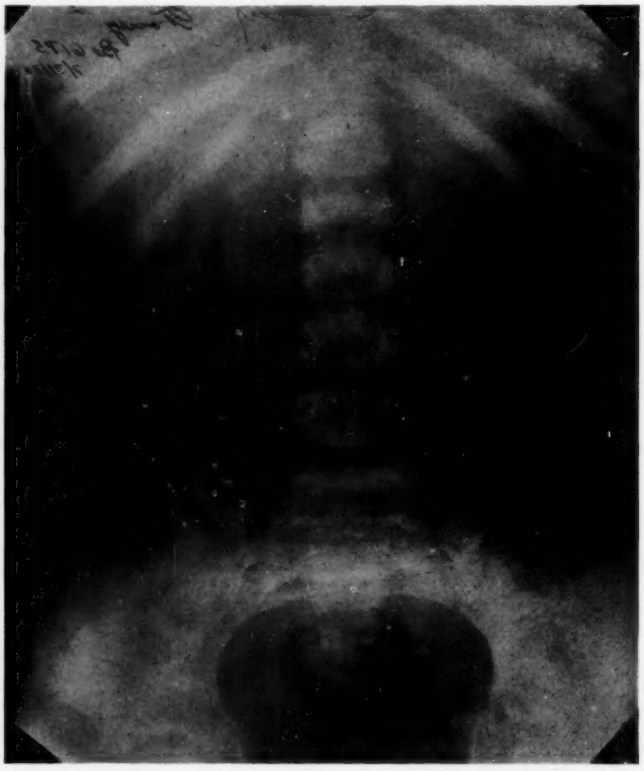


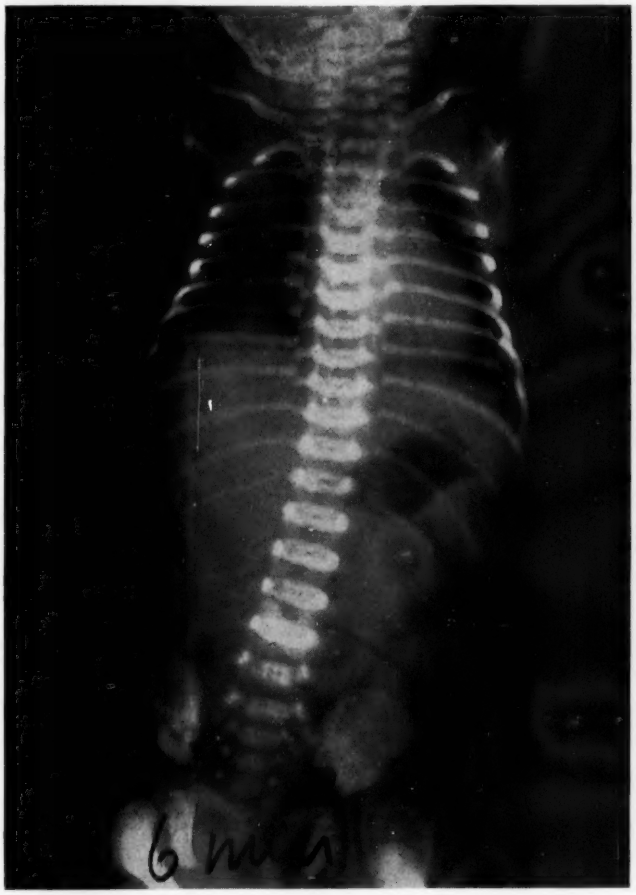
Fig. 2.—Roentgenograms of the abdomen of a 10-year-old child. Some gas is seen in the ascending colon and a greater quantity in the descending colon. None can be seen in the small bowel.

Thiele made x-ray examinations of 4 infants immediately after birth to determine how soon gas entered the gastrointestinal tract. In 1 instance, seven minutes after birth no gas was seen in the stomach or intestine, but in the other 3 cases at seven, ten, and thirty-five minutes after birth respectively gas was found to be present in the stomach or stomach and bowel.

Soveri injected air into the stomachs of infants and observed on roentgenograms the rate of its passage through the gut. Approximately thirty minutes was required for the stomach to empty itself of

injected air. Within one to two hours the small bowel was usually empty also. If the intestinal canal was empty, gas passed through the colon in one to two hours, but usually a slower rate prevailed.

The observations which are reported here were made with two questions in mind. It was desired to determine if accumulations of gas visible on the x-ray film were consistently found in the small bowel of infants and children and if so at what age these shadows disappeared. The second question was how soon after birth gas could be detected in the gastrointestinal tract by x-ray examination and how quickly transport of this gas through the bowel into the sigmoid colon and rectum occurred.



A.

Fig. 3*A-C.*—Serial x-ray films of a normal newborn infant. *A.* Six minutes after birth gas can be seen in the stomach.

METHODS OF OBSERVATION

To determine the distribution of gas in the small bowel of infants and children 46 patients on the Pediatric Wards of the University of Minnesota Hospitals were chosen. These patients were selected care-

fully to exclude any condition which might occasion the presence of inhibitive (paralytic) ileus or other conditions affecting the bowel. In most instances observations were made a day or so before discharge. All of the older children were ambulatory at the time of the examinations. Without any preparation roentgenograms of the abdomen were made in the supine position. These films were then studied to determine the location of the intestinal gas.

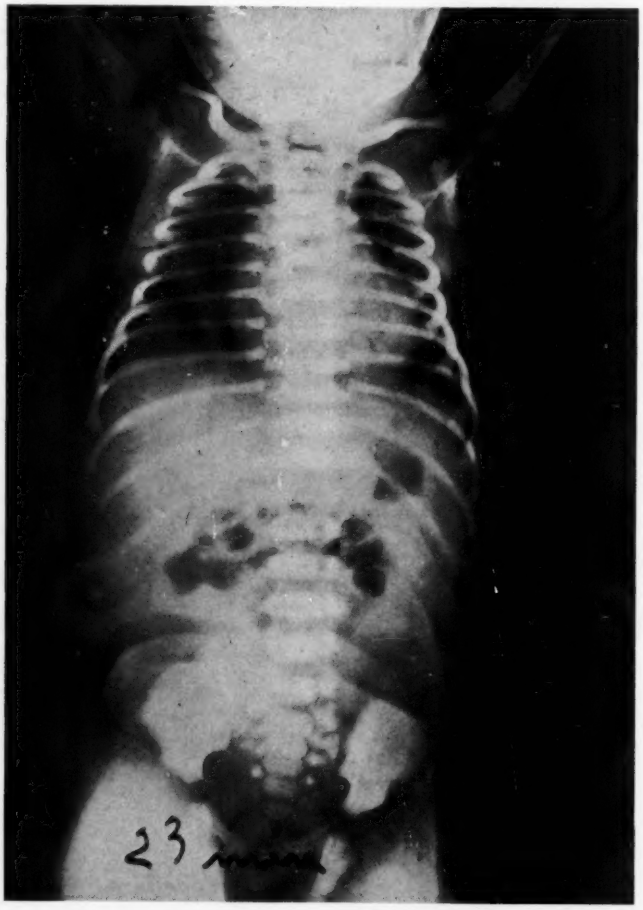


Fig. 3*B*.—Twenty-three minutes after birth the amount of gas in the gastrointestinal tract has increased. Accumulations in the jejunum as well as the stomach can be seen.

In order to determine the time of appearance and speed of transport of gas through the gastrointestinal tract of newborn infants a series of roentgenograms was made for each of 7 normal babies in the Pediatric Nursery of the University of Minnesota Hospitals. The birth of each of these infants was uncomplicated. An attempt was made to take the first film as soon after birth as possible. Additional films were made at chosen intervals of time. Except for changes in position made necessary by their care these infants were all kept in the supine position during the period of the observations.

DISTRIBUTION OF GAS

In Table I are listed the various conditions present in the 46 patients in whom the distribution of gas in the gastrointestinal tract was studied.

TABLE I

DIAGNOSIS	NUMBER OF PATIENTS
Normal infant	28
Asthma	1
Diabetes mellitus	2
Eczema	2
Injury of right eye	1
Strabismus	2
Congenital cleft palate	3
Congenital cleft lip	1
Pes cavus	1
Spastic paralysis	1
Talipes equinovarus	2
Tuberculous cervical adenitis	1
Torticollis	1

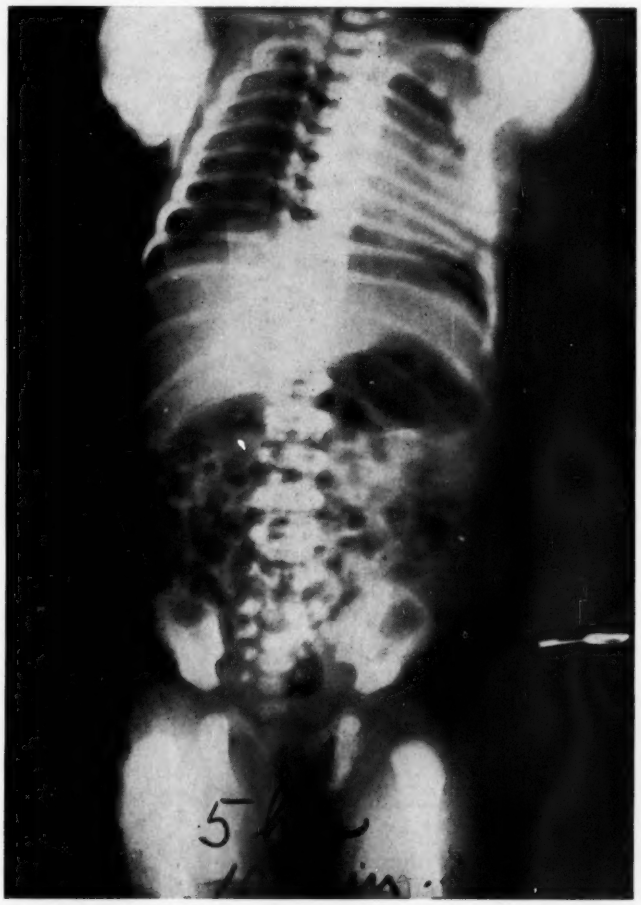


Fig. 3*C*.—Five hours and ten minutes after birth, gas has passed through the whole gastrointestinal tract. A small quantity can be seen in the rectum.

The distribution of the gas in the gastrointestinal tract as seen on roentgenograms is indicated in Table II.

TABLE II

DISTRIBUTION OF GAS IN THE GASTROINTESTINAL TRACT OF INFANTS AND CHILDREN

PATIENT	AGE OF PATIENT	DISTRIBUTION OF GAS	
		SMALL INTESTINE	COLON
1	Newborn	++	++
2	Newborn	++	++
3	Newborn	++	++
4	Newborn	++	++
5	Newborn	++	++
6	Newborn	++	++
7	Newborn	++	++
8	Newborn	++	++
9	Newborn	++	++
10	6 hr.	++	++
11	6 hr.	++	++
12	1 day	++	++
13	3 days	++	++
14	4 days	++	++
15	6 days	++	++
16	6 days	++	++
17	7 days	++	++
18	7 days	++	++
19	8 days	++	++
20	9 days	++	++
21	9 days	++	++
22	10 days	++	++
23	2 wk.	++	++
24	2 wk.	++	++
25	2 wk.	++	++
26	2 wk.	++	++
27	2 wk.	++	++
28	2 wk.	++	++
29	5 wk.	++	++
30	10 mo.	++	++
31	10 mo.	++	++
32	13 mo.	+	+++
33	17 mo.	++	++
34	18 mo.	+	+++
35	21 mo.	+	+++
36	2 yr.	+	+++
37	2 yr.	+	+++
38	3 yr.	+	+++
39	3 yr.	+	+++
40	6 yr.	0	++++
41	7 yr.	+	+++
42	7 yr.	+	+++
43	7 yr.	0	++++
44	8 yr.	0	++++
45	9 yr.	0	++++
46	10 yr.	0	++++

DISCUSSION

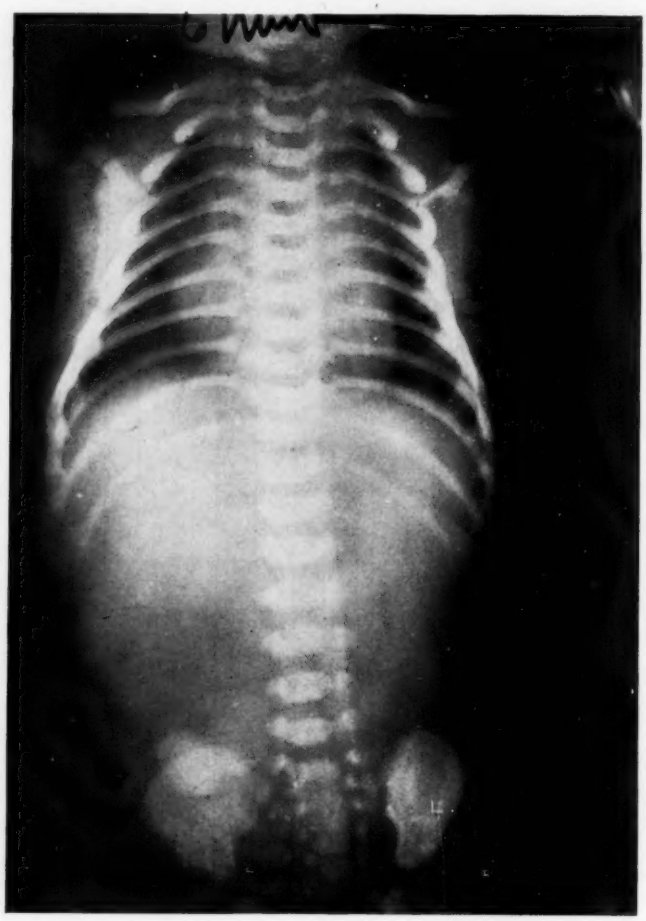
These results indicate that in infants under 18 months of age the gas present in the gastrointestinal tract which can be demonstrated by x-ray examination is about equally distributed between the small and large bowel. Between the ages of 18 months and 6 to 7 years this distribution gradually changes so that more of the visible gas comes

TABLE III

THE TIME OF APPEARANCE AND TRANSPORT OF GAS THROUGH THE GASTROINTESTINAL TRACT OF NEWBORN INFANTS AS DETERMINED BY SERIAL ROENTGENOGRAMS

CASE NO.	STOMACH	DUODENUM	JEJUNUM	ILEUM	CECUM	ASCENDING COLON	TRANSVERSE COLON	DESCENDING COLON	SIGMOID COLON	RECTUM
1	6 min.		1½ hr.	2½ hr.						4½ hr.
2	10 min.		50 min.	2¼ hr.		4½ hr.			6 hr.	
3			15 min.	40 min.			2¼ hr.			4 hr.
4		6 min.	30 min.	1 hr.			2 hr.	3 hr.	4 hr.	
5			15 min.		45 min.		1½ hr.	3 hr.	4 hr.	
6		8 min.	30 min.	2½ hr.		3½ hr.			4½ hr.	
7	6 min.		40 min.	2 hr.				4¾ hr.		5 hr.

to be present in the colon. After 6 to 7 years of age practically all the visible gas is seen in the colon. These observations furnish no information to explain this change in gas distribution. The importance of these facts in the diagnosis and treatment of intestinal obstruction in infants and children is obvious, however, for in such patients the presence of visible gas in the small bowel cannot be assumed to be necessarily due to intestinal stasis as is the case with older children



A.

Fig. 4*A-C.*—Serial x-ray films of a normal newborn infant. *A.* Six minutes after birth, a small quantity of gas can be seen in the stomach.

and adults. This is not to say that roentgenograms of the abdomen are not of any value in cases of obstruction in infants and young children, but rather that they must be interpreted with care and with due allowance for the facts here brought forth. In the presence of small bowel obstruction the amount of gas present in the small bowel will be larger than normal and the diameter of the gas-filled coils will be greater.

TIME OF APPEARANCE AND SPEED OF TRANSPORT OF GAS IN THE GASTROINTESTINAL TRACT OF NEWBORN INFANTS

In Table III are presented the results of observations made in the course of a series of roentgenograms of the abdomen of 7 newborn infants. The first film in each series was taken as soon as possible after birth. The time indicated is the interval after birth at which the x-ray film was made. The portion of the gastrointestinal tract indicated is the most distal portion of the bowel in which gas could be seen.

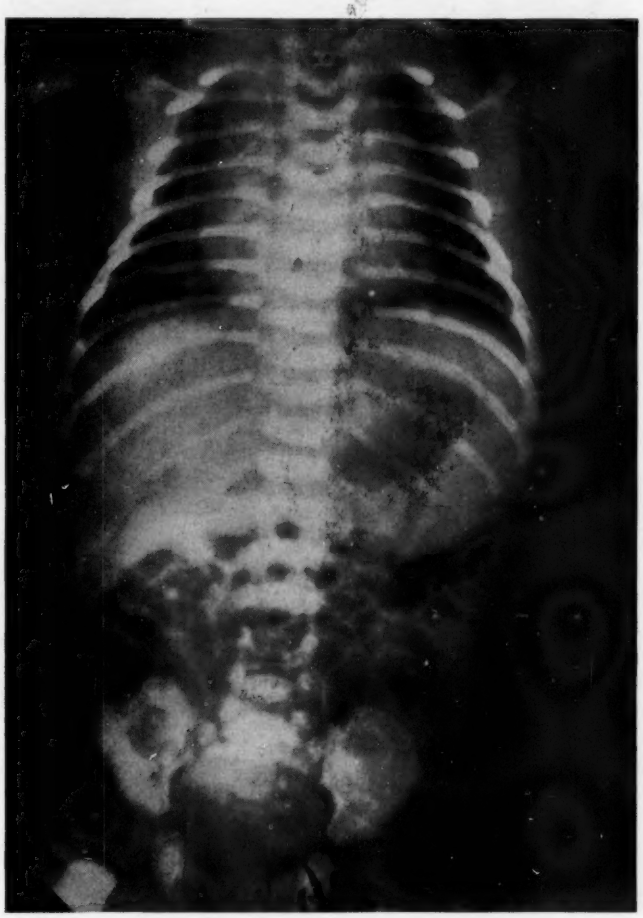


Fig. 4*B*.—After two and one-half hours, gas has passed down into the ileum.

DISCUSSION

The rapid appearance of gas in the stomach and upper gastrointestinal tract in newborn infants as shown in Table III gives further confirmation to the swallowed air theory of the origin of most intestinal gas. The important fact with respect to intestinal obstruction in the newborn, such as congenital atresia of the small bowel, is that within four to six hours after birth one should regularly find gas in the sig-

moid colon and rectum. If the presence of a congenital type of obstruction is suspected the diagnosis may be confirmed much earlier if this fact is remembered.

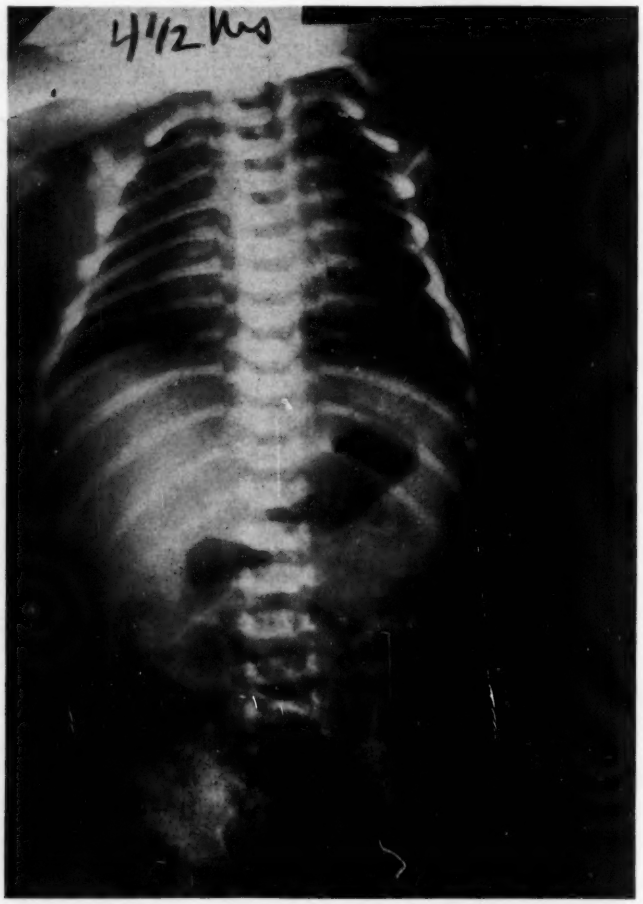


Fig. 4*C*.—After four and one-half hours, a large quantity of gas can be seen in the rectum. Other accumulations are scattered through the entire gastrointestinal tract.

In another respect the transport of gas to the rectum within six hours is important. This has to do with cases of imperforate anus and atresia of the rectum. Wangensteen and Rice in 1930 described a means by which the length of the atresic portion of the anus and rectum could be determined. The infant is held in the inverted position and the mercury bulb of a thermometer is pressed into the anal dimple or passed into the rectum up to the area of atresia. If a roentgenogram is then taken, the distance between the gas shadow proximal to the atresia and the radiopaque mercury bulb gives an accurate idea as to the length of the atresic gut. Consequently the magnitude of the operative procedure which will be necessary to correct the defect may be accurately judged. Every surgeon of experience will appreciate the importance of such information before a contemplated operation.

The validity of this maneuver depends of course on the correctness of the assumption that gas has progressed up to the point of obstruction at the time the x-ray film is made. The observations here reported indicate that this test cannot be depended upon until the infant is 6 or more hours old. Whether or not the presence of the obstruction and retained meconium will increase the time interval before gas arrives at the point of obstruction is not known.

SUMMARY

Roentgenograms of the abdomen were made on 46 children varying in age from a few minutes to 10 years. All these infants were thought to have normally functioning gastrointestinal tracts. The distribution of the intestinal gas with respect to the small bowel and colon was studied and the following information obtained:

1. Up to 18 months of age gas is distributed about equally between the small bowel and the colon.
2. Between 18 months and 6 years of age more and more intestinal gas is found in the colon and less in the small bowel.
3. After 7 years of age, as in adults, no gas in the small bowel is seen on the x-ray film.

Serial roentgenograms of the abdomen were made on 7 newborn infants. The first film in each case was made as soon after birth as possible and others at convenient intervals. On these films the interval after birth at which gas appeared in the gastrointestinal tract and the speed of its transit to the rectum were studied. In each case gas was observed to be already present in the stomach, duodenum, or jejunum by the time the first film could be taken which was within six to fifteen minutes after birth. Within four to six hours after birth gas was present in the sigmoid colon or rectum.

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CYSTIC DEGENERATION OF THE OVARIES*

An Experimental Study

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OVARIAN cysts have interested medical authors for many years, and since Rokitansky's description[1] of cystic disease, numerous reports of ovarian conditions have appeared. Cystic degeneration of the ovaries has been repeatedly described under such terms as chronic oophoritis, sclerocystic oophoritis, cirrhosis of the ovary, and hydrops ovarii folliculi. In spite of the multiplicity of reports, the etiology of this condition has never been accurately determined. Earlier reports[1-4] have indicated that chronic infection of the ovary produced cystic changes. A few authors[5, 6] have comparatively recently ventured support of this theory. The consensus today is opposed to this view. Another theory as to the etiology of this state supported by continental investigators[7, 8] has proposed that sympathetic dysfunction will result in multiple ovarian cysts. With the advent of hormonology, the current trend of thought is to explain cystic degeneration of the ovaries upon an endocrinologic basis, primarily pituitary in origin. Investigators[9-13] have been able to cause rapid follicular growth and atresia by the use of pituitary implants and extracts. However, these changes have not proved to be permanent.

Interest in this problem was stimulated when several cases of young women with large prolapsed multicystic ovaries were observed. It was noted that when this condition obtained, there was associated with it extensive congestion in the veins of the infundibulopelvic and broad ligaments. This suggested the possibility that the underlying cause of the ovarian change was the altered position and vascularity of the gland, rather than an extrinsic factor.

The anatomic relationship of the ovary has been adequately described, and the vascular supply has been exhaustively studied by Sampson.[14] However, the effects of circulatory impairment have not received a great deal of attention. Butcher,[15] with ligation experiments, showed that germ cells have little resistance and soon perish, whereas the germinal epithelium may survive later to replenish the germ cells when collaterals are fully developed. Neugebauer,[16] likewise, showed that extensive necrosis with loss of function followed ligation of ovarian vessels. The question as to whether hysterectomy will ultimately lead to cystic degeneration of the ovaries has been debated by many authors without any

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substantial proof that such a result will occur. Recent authors[17-19] have agreed that hyperemia of the ovary resulting from congestion is a probable cause of cystic degeneration by causing increased follicular activity.

Since no experimental support to this contention has been offered, it was felt that prolapse of the ovaries of animals artificially produced would cause passive vascular congestion. The ovarian changes resulting from such a procedure would indicate what effect hyperemia produced upon the follicular apparatus.

EXPERIMENTAL PROCEDURE

To study the effect of circulatory impairment upon the ovary caused by prolapse of the organ, two groups of animals were used. Rabbits and dogs were selected because of the ease of procurement and management, although they lacked the cyclic changes found in the primates.

Fig. 1.—Normal rabbit ovary. The section shows normal ovarian stroma with healthy primordial and vesicular follicles.

I. *Rabbits.*—In order to study the effect of circulatory impairment on rabbit ovaries, ligation experiments were performed on several groups of animals, by ligating the ovarian vessels on the utero-ovarian anastomosis on both sides. All animals were segregated and sacrificed after twelve weeks. Sections of each ovary were compared to sections of ovaries of normal rabbits (Fig. 1). The results conformed with those reported by Butcher and Neugebauer.

In other groups of animals (one to four in a group) partial deprivation of the vascular supply of both ovaries as well as artificial prolapse

of the organ was produced. In all of these animals, changes in the follicular apparatus corresponded to those in which ligation alone was performed.

Finally artificial prolapse of the ovary without impairment of the circulation was secured by suturing the free (antimesenteric) border of the ovary to the lateral abdominal wall. Sutures were introduced through the tunica albuginea opposite the hilum, avoiding the hilar vessels. In such a way each ovary was displaced from the paravertebral gutter to a new position about one inch lateral and vertical to its normal bed. All animals were sacrificed after twelve weeks.

Results.—In those rabbits whose ovarian vessels were ligated extensive necrosis occurred in the ovary, marked by fibrosis, loss of follicular structure, and fibrinous deposits on the tunica albuginea. In some animals, the degeneration was not marked, involving only the follicular apparatus, with pyknosis of the ovular and granulosa cell nuclei.

Fig. 2.—Prolapsed rabbit ovary. The section shows cystic follicles lined with degenerate granulosa cells. The primordial follicles are atretic, and there is an increased fibrosis of the stroma.

In those animals in which the utero-ovarian anastomosis was ligated, similar changes were noted. All ova were degenerate, and atresia of the large follicles in which ova could not be demonstrated showed pyknosis of granulosa cell nuclei. Few prevesicular follicles were noted, and all follicles in the vesicular stage were atretic.

Artificial prolapse of the ovary, without vascular ligation, resulted in a somewhat different pathologic picture. Healthy follicles, both primordial and prevesicular, were demonstrable in all sections, but many

of each group showed atretic changes. All vesicular follicles were atretic, and many of these were markedly dilated (Fig. 2). The ovum was usually absent in the large follicles and, when present, exhibited coagulation necrosis of the cytoplasm and nuclear fragmentation. Many large spaces were lined with theca interna, having lost the granulosa

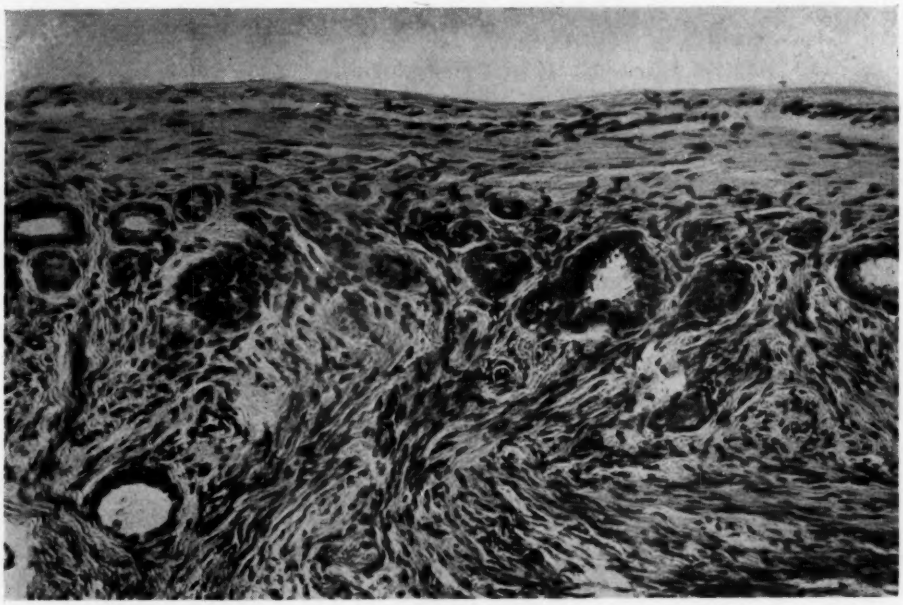

Fig. 3.—Control dog ovary. A section through the cortex shows healthy primordial follicles and the normal thickness of the tunica albuginea.

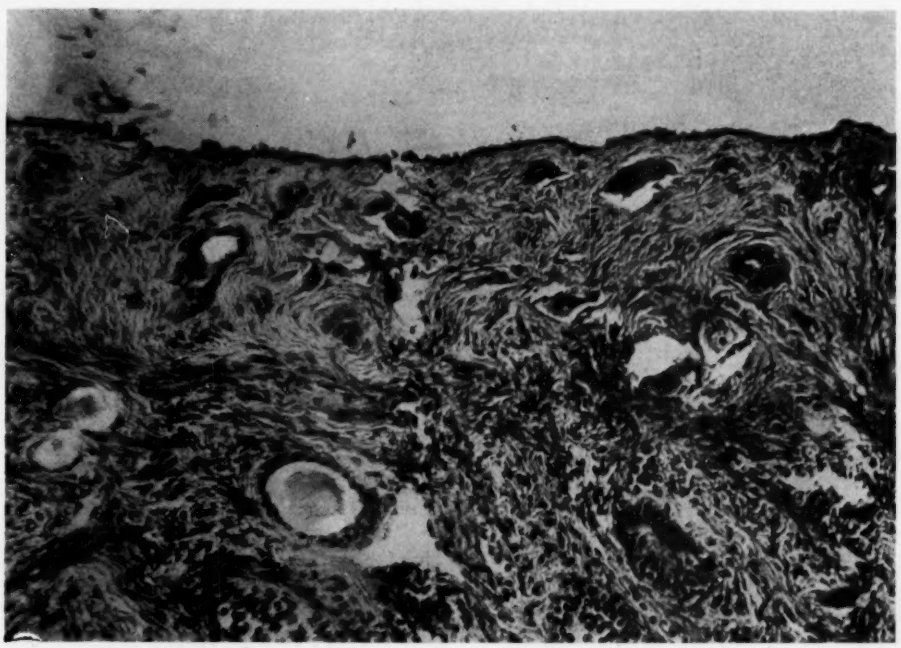

Fig. 4.—Prolapsed dog ovary. This section, under the same magnification as Fig. 3, shows the marked fibrosis of the tunica albuginea as a result of the prolapse. Many atretic primordial follicles can be seen.

cell lining entirely. Aside from the extensive damage to the follicular apparatus, artificial prolapse produced vascular congestion in the medulla. Numerous dilated capillaries could be seen beneath the cortex. The tunica albuginea was thickened in many instances.

II. *Dogs.*—On a group of eleven dogs the left ovary was artificially prolapsed in a similar manner without vascular ligation. The right ovary was maintained in a normal position as a control. As in rabbits, the animals were castrated after twelve weeks, and sections of each ovary were studied.

RESULTS.—Examination of the dog ovaries did not show as striking changes as did those of the rabbit. The damage produced by artificial prolapse again centered around the follicular apparatus with congestion and fibrosis of the tunica albuginea secondarily. Again atresia was most evident in the larger vesicular follicles, although a greater number of atretic primordial follicles were noted in the prolapsed ovary. The large follicles were cystic, exhibiting no ovum, and degenerative changes were present in the granulosa cell layer when it was present. Capillary congestion was marked, and perifollicular edema was present. The tunica albuginea was thickened and fibrotic in almost all of the prolapsed ovaries (Figs. 3 and 4).

DISCUSSION

The changes produced in the experimental animals by artificial prolapse are chiefly vascular and affect the vesicular follicle primarily, producing follicular cysts. Small follicles are damaged to a lesser extent. Likewise an increased thickness of the tunica albuginea results from the altered position.

Such a picture is seen in the human ovary with cystic degeneration. Almost all follicles are large and atretic, with or without granulosa cells lining them. Smaller follicles are occasionally found, usually unaltered. Vascular congestion is prominent and thickening of the tunica albuginea is present, sometimes to a marked degree.

The presence of many follicular cysts in cases of cystic degeneration is evidence that normal maturation of the follicle does not occur in these individuals. Normal growth occurs to a point prior to maturity, but rupture of the follicle rarely occurs. Menstruation therefore is anovulatory in type. When cystic degeneration is fully developed, amenorrhea and menometrorrhagia develop, one following the other. Because of the menstrual disturbance and the anovulatory bleeding, sterility is a common complaint.

Treatment of cystic degeneration of the ovaries has varied from ignipuncture to removal. The former does not afford complete relief and the latter is too radical. Hormonal therapy, unfortunately, is not usually successful as many attest. Best results are obtained by partial resection of the ovaries with suspension.[8, 20-24] Partial resection removes

the multicystic nonfunctioning area, as well as a large part of the thickened tunica albuginea. Suspension of the ovaries prevents the passive congestion with its secondary effects. Troublesome adhesion formation along the line of resection can be prevented by tying an omental graft along the suture line. It has been experimentally demonstrated that partial resection leaves a functioning ovary without undue destruction of the gland.[25] In 14 cases, restoration of function occurred in 10, partial success in 2, and failure in 2.

CONCLUSIONS

1. Cystic degeneration of the ovaries, formerly thought to be the result of chronic infection, is now variously ascribed to sympathetic dysfunction and hormonal imbalance. Circulatory impairment is an infrequently considered but important etiologic factor.

2. Circulatory impairment was produced in the ovaries of eighteen rabbits by (1) vascular ligation and (2) artificial prolapse, and in one ovary of eleven dogs by artificial prolapse. Sections of these ovaries showed changes in the follicular apparatus analogous to those found in human ovaries with cystic degeneration.

3. The treatment giving the best results is partial resection and suspension of such cystic ovaries.

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Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

THE SPHINCTER MECHANISM OF THE COMMON BILE DUCT IN HUMAN SUBJECTS

ITS REACTIONS TO CERTAIN TYPES OF STIMULATION*

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DURING the past few years new methods of investigation have led to great advances in the understanding of the activity of the human gall bladder and its relation to the discharge of bile into the duodenum. Until very recently, however, knowledge of the physiology of the sphincter of Oddi has been based largely upon the results of animal experimentation.

The discharge of bile into the duodenum is dependent upon the pressure of bile secretion, the activity of the gall bladder, and the tonus of the sphincter of the common duct. It is clear that deductions concerning sphincter activity cannot be made from observations of the amount of bile aspirated from the duodenum, since the relative importance of other factors regulating flow cannot be estimated under such conditions. Only direct measurements of sphincter tone are of value. Such measurements cannot be made in entirely normal individuals, but information can be secured from studies upon patients with intubation of the common bile duct. By investigations upon such subjects many significant observations have been made.

There are marked species differences between the sphincter of Oddi of man and that of the common laboratory animals, and, on the basis of structural differences, anatomists have anticipated that the activity of the human sphincter would differ in some respects from that of animals. While this review will contain references to experiments carried out upon animals, it will be concerned chiefly with the responses of the human sphincter to various types of stimulation and will include a report of the findings of a series of experiments which I carried out at the University of Minnesota.

*This review includes material presented in a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Ph.D. in Surgery, May, 1940. Protocols of individual experiments may be found in the original thesis.

HISTORICAL SKETCH

Although attention has been devoted to the biliary tract since antiquity, an accurate knowledge of even the gross anatomic characteristics of this region was not acquired until the work of Vesalius (1543).[223] According to Boyden,[36] Vesalius recognized that some mechanism impeded the flow of bile from the choledochal orifice, but he did not identify an anatomic sphincter of the bile duct. The credit for first describing such a sphincter is extended to Glisson (1654),[84] who recognized "ring-like fibers" around the terminal portion of the duct.

Following Glisson, Bianchus (1711)[27] suggested the importance of contraction of this sphincter as a mechanism contributing to the filling of the gall bladder.

The American anatomist, Gage (1879), was the first to study the sphincter of the bile duct microscopically.[80] Oddi (1887), for whom the muscle has been named, carried out gross and microscopic investigations, and also was the first to study the function of the sphincter.[176-180] He noted the resistance to the flow of fluid which the sphincter mechanism exerted, and he observed the dilatation of the bile ducts which followed cholecystectomy in certain animals. He suggested that spastic contraction of the muscle might explain obscure clinical types of jaundice.

Morgagni (1761) had discussed the possible clinical significance of spasm of the bile duct more than a century before the time of Oddi,[164] but it is obvious from his writing that he had no clear understanding of the minute anatomical arrangement which might allow such a spasm to occur. He wrote concerning the rarer causes of jaundice: "I speak of spasmodic crispatures, by which, at least, the orifice of the common duct, or the greater part of the small branches of the hepatic are constringed."

Although Oddi stated that he had extended his observations to include man, his descriptions were based upon his investigations in animals, and Znaniecki (1895) has been credited with being the first to describe the human sphincter histologically. The detailed study of Hendrickson (1898) appeared three years later.[99] Since that time a number of investigators, including Letulle and Nattan-Larrier,[134] Helly,[98] Job,[118] Mann,[154] Giordano and Mann,[83] Nuboer,[173, 174] Porsio,[186] Ivy,[106-114] and others have contributed further anatomical and physiologic data.

Present-day knowledge of the anatomy of the sphincter has been increased greatly by the contributions of Boyden and his associates,[34-48, 209-211] who have studied extensively its embryologic development as well as its structure in the adult.

ANATOMICAL CONSIDERATIONS

The terminal portion of the common bile duct courses obliquely for a distance of 1 to 2 cm. through the duodenal wall before opening into the

intestinal lumen. In this region it is accompanied by the principal pancreatic duct (Wirsung), and the two ducts usually unite (ampulla of Vater) just before emptying into the duodenum at the papilla major.* This papilla is about 8 or 10 cm. from the pylorus and is located just above or just below a constant bend in the pars descendens of the duodenum which Schwegler and Boyden[209-211] have designated as the biliary flexure.

The intramural portion of the bile duct is considerably narrower than the extramural portion. Baggenstoss[4] attributes this to the distribution of the sphincteric and duodenal musculature, and also to the increased thickness of the mucous membrane in this region.

Schwegler and Boyden[209-211] have traced the development in the embryo, and have observed that, although the ampulla is at first coextensive with the oblique intramural passage of the duct through the duodenum, it later recedes (beginning at the 20 mm. embryo stage) and near term it lies halfway between the tunica muscularis and the end of the papilla. Mann and Giordano,[156] in material obtained at autopsy, showed that in 76 per cent of their cases the ampulla of Vater was 2 mm. or less in length. In spite of this involution, the ampulla is an important structure because it gives rise to folds or valvules which prevent the regurgitation of intestinal contents into the ducts.

As the bile duct and pancreatic duct enter the duodenal wall, they pass through a lengthwise hiatus in the longitudinal muscle and a transverse, eye-shaped fenestra in the circular muscle.† In the adult these slits have become narrow and have been filled partly by muscle bands that have grown in from the margins.

Boyden[128] has classified the muscles of the choledochoduodenal junction into (1) muscles of the choledochoduodenal aperture and (2) intrinsic muscles of the ducts and ampulla.

The former group includes the superior and inferior margins of the choledochal fenestra (which impinge on the ducts at only one level and differ in this respect from the anatomical arrangement in animals such as the dog), the reinforcing or R-fibers and the connecting or C-fibers. The R-fibers reinforce the angles of the fenestra, while the C-fibers connect the margins of the hiatus and fenestra with the papilla and the ducts.

The intrinsic muscles of the ducts and ampulla include: (1) the sphincter choledochus, (2) the longitudinal fascicles, (3) the sphincter pancreaticus, and (4) the sphincter ampullae.

The sphincter choledochus is the most highly developed portion of the intrinsic sphincter of Oddi. It consists of an annular sheath of

*The bile duct and pancreatic duct do not always have a common opening into the duodenum. Mann and Giordano[156] found separate openings in 31 per cent of 200 cases. Baggenstoss[4] collected reports describing 1,001 specimens, and in that group 43 per cent did not show an ampulla.

†The anatomical terms used in this description are those which have been accepted or introduced by Boyden and his associates.

muscle fibers surrounding the bile duct from a position just outside the window to the junction with the pancreatic duct. It is capable of obstructing the flow of bile without closing the pancreatic duct. In fact, Boyden[41] recently has described a case in which this muscle held a stone in the major papilla until it was too large to pass the orifice and was about to be discharged through a spontaneously developed fistula when the patient died.

The fasciculi longitudinales consist of two columns of longitudinal fibers lying between the choledochus and the pancreatic duct. They are made up of bands connecting different transverse levels of the ducts and ampulla and they are joined by the C-fibers. They probably serve to erect the papilla and thus facilitate the discharge of bile.

The sphincter pancreaticus is an annular band of fibers around the lower end of the pancreatic duct. It is not constant.

The sphincter ampullae is an annular sheath of fibers surrounding the ampulla, when the latter structure is present, and also encircling the lower end of the bile and pancreatic ducts. Kreilkamp and Boyden[128] found it to be well developed in only one-sixth of adults. Contraction of this muscle prevents the flow of bile and pancreatic juice into the duodenum and may permit the reflux of bile into the pancreatic duct or of pancreatic juice into the bile duct.

PHYSIOLOGIC CONSIDERATIONS

Anatomists[209-211] have demonstrated beyond question the independent origin of a distinct sphincter at the terminal portion of the common bile duct, and Layne and I[14, 132] have presented evidence to show that the sphincter of Oddi also functions independently of the duodenal musculature in man.

Giordano and Mann,[83] Lueth,[138], and Sandblom, Voegtlin, and Ivy[200] have observed an independent action of the sphincter in animals, but these same investigators, as well as others (Copher and Kodama,[61] Elman and McMaster,[75] Burget,[52] Brugsch and Horsters[50]), have demonstrated that, in animals, duodenal motility and tone exert a powerful influence on the flow of bile into the duodenum. To explain species differences in reactions, Boyden[37] has pointed out that there are marked species differences in the arrangement of the intestinal muscle around the bile ducts as well as in the intrinsic musculature. He states that: "In man, the window in the duodenal muscle through which the bile and pancreatic ducts enter the intestine is of such shape and size that duodenal peristalsis exerts a minimal effect on the flow of bile. By contrast the duodenal window of the dog has the shape of a funnel which envelops the first two-fifths of the intramural course of the bile duct."

On the other hand, McGowan, Knepper, Walters, and Snell[149] demonstrated, in a group of patients with postcholecystectomy colic, that spasm of the duodenum was associated with attacks of pain resembling

biliary colic, and that this pain could be relieved by intubation of the common bile duct. But the possibility remains that in their experiment both the pain and the simultaneous rise in the intraductal pressure may have been due to contraction of the sphincter within a spastic segment of the duodenum.

From the data presented by Layne and myself,[14, 132] one may conclude that, in man, the sphincter of Oddi does function independently. It is difficult to rule out entirely the factor of duodenal tone and motility in determining the resistance to the flow of bile, but anatomical observations indicate that it must be much less important in man than it is in animals. When we speak of the sphincter in a physiologic sense, however, we refer to the entire intramural regulatory mechanism, including both the action of the intrinsic sphincter and any influence which might be exerted by the muscle of the intestine.

The first activity to be attributed to the sphincter mechanism was the prevention of regurgitation of duodenal contents into the common bile duct (Glisson, 1654), and this is still regarded as one of its functions, although the mucosal folds or valvules arising in the ampulla may be even more important in accomplishing this. When the sphincter action is eliminated, such as occurs in cases of internal biliary fistula, some degree of ascending infection follows.[199] This infection is usually slight and produces no clinical effect, but occasionally it may be severe. Wangensteen[237] has pointed out that an adequate stoma decreases the danger of cholangeitis following anastomotic operations uniting the biliary tract and the gastrointestinal canal, but that narrowing or partial occlusion of the stoma favors infection. Recent experimental studies of Bachrach and Fogelson[3] substantiate Wangensteen's observation.

Gorham and Ivy[87, 88] have found that in some animals devoid of a competent sphincter there are other mechanisms for preventing regurgitation. There may be a one-way valve (as in the horse), large quantities of hepatic bile may keep the ducts flushed out (as in the horse and pigeon), or the extrahepatic ducts may show peristaltic activity (as in the pigeon).

A second function of the sphincter is to regulate the flow of bile into the intestine. The liver secretes bile continuously, but the latter is admitted to the duodenum only intermittently, depending upon the state of contraction of the gall bladder and of the sphincter of the bile duct. Whether or not the gall bladder evacuates when stimulated depends upon the resistance to flow of bile from the common duct into the duodenum. The maximum expulsive force of the gall bladder is 30 cm. of bile pressure,[106] while a spastic sphincter can resist a considerably greater force. If one grants that the gall bladder serves for the storage of bile for digestive purposes (and there is much evidence to support such a contention[87, 88]), this regulatory function of the sphincter is of considerable importance.

A third function of the sphincter is to aid in filling the gall bladder. If the sphincter mechanism be destroyed, the gall bladder does not fill and the bile flows directly into the intestine. Some physiologists believe that the chief function of the gall bladder is as a pressure regulatory mechanism to prevent the intraductal pressures from rising too high at times when the sphincter is closed. If such be the case, this third function of the sphincter is secondary to the function of preventing duodenal regurgitation, but if concentrated gall bladder bile has any advantage over unconcentrated hepatic bile in the processes of digestion, the part played in the filling of the gall bladder is an important function of the sphincter of Oddi.

A fourth function, attributed to the joint action of the longitudinal fascicles and the C-fibers, is to erect the papilla and facilitate the discharge of bile into the duodenum.

The extent of nervous control of the sphincter of Oddi is still not settled. The so-called Doyon-Meltzer law of reciprocal innervation of the gall bladder and sphincter of Oddi maintains that when the gall bladder contracts the sphincter relaxes as a result of reflex excitation, and during the storage of bile the sphincter is contracted and the gall bladder is relaxed. Evidence does indicate that there is a relationship between gall bladder and sphincter activity, but the mechanism of this relationship is not yet clear and the part played by the nervous system is not known. Some experimental evidence[70, 106, 138, 240] indicates that nervous regulation of the sphincter may be important in animals. Boyden,[38] however, suggests that nervous control of this muscle in man is probably less important than hormonal control. He has demonstrated that while experimentally induced spasm of the stomach will inhibit gall bladder evacuation in animals, this effect is not obtained in man. Furthermore, I[9, 12] have shown that the human sphincter of Oddi responds to a fatty meal even after the gall bladder has been removed, indicating that relaxation of the sphincter under such circumstances is not dependent upon a reciprocal relationship as postulated by the Doyon-Meltzer concept.

Recently Reich[197] has reported one human case in which he sectioned the descending nerve on the posterior aspect of the hepatic artery in an attempt to decrease sphincter tone. He reported that the procedure produced a decreased sphincter resistance and an altered response to the injection of morphine. Boyden[40] has pointed out that there are objections to accepting Reich's report as evidence of nervous control of the sphincter in man; and one of his students recently has demonstrated that elimination of the specific ("gastroduodenal") nerves to the choledochoduodenal junction markedly retards evacuation of the biliary tract (Johnson, 1941). Furthermore, subphrenic severance of the splanchnic roots of the celiac ganglia in these animals produces the

opposite effect, namely slight acceleration of flow, but it is believed that this is due to section of nerves inhibiting the gall bladder reflexes which are not present in man.[45]

Painful sensations identical with biliary colic may be produced by spastic contraction of the sphincter of Oddi in man. This was demonstrated first by Ivy, Voegtlin, and Greengard (1933), who produced such a spasm in a single case by the injection of a secretin-cholecystokinin preparation,[114] and later by Butsch, McGowan, and Walters,[55] who observed colic in patients with sphincter spasm resulting from the administration of morphine. Zollinger[246] and Layne and Bergh[13, 132] have produced sphincter spasm associated with colic by sudden distention of the bile ducts. The pain in some cases remains localized in the epigastrium or right hypochondrium, while in other cases there is radiation to the interscapular or right subscapular region. Associated with the pain there is rigidity of the muscles of the abdominal wall, greatest in the right upper quadrant, and there may be inspiratory distress, and occasionally nausea and vomiting.[9]

Schrager and Ivy[207] have demonstrated that in animals similar pain responses may be abolished by splanchnic section, nausea and vomiting may be abolished by section of the vagi, and the respiratory disturbances are reduced by section of either the splanchnics or vagi. There is very little information concerning the sensory innervation of the sphincter area in man, but it has been assumed to be similar. Snell, McGowan, and Butsch[215] have reported three patients upon whom right splanchnic section was undertaken in an attempt to relieve postcholecystectomy pain. The results were satisfactory in one case and unsatisfactory in two. The failures were explained on the ground that the left splanchnic nerves, which had not been sectioned, may have carried sensory fibers. The more recent experiments of Boyden and Johnson[45] would indicate that persistence of pain might also be due to failure to interrupt the lesser splanchnic and first lumbar roots of the celiac plexus.

METHOD OF MEASURING SPHINCTER RESISTANCE

The sphincter resistance may be measured in patients with intubation of the common bile duct by a method similar in its essential principles to that employed in animal experiments by Mann,[153] Elman and McMaster,[75] and others.

My studies were carried out upon patients who previously had undergone cholecystectomy, choledochotomy, and intubation of the common bile duct. As a preliminary procedure the anatomical status of the bile ducts was demonstrated to be normal by cholangiographic examination. Several weeks were allowed to intervene between the operation and the time of the experiments, and the studies were carried out after the patients had fasted for eight hours. The investigations caused the

subjects, no discomfort and anesthesia was not required. The patients rested quietly in bed in the supine position throughout all procedures.

The apparatus, which was sterilized in the autoclave, consisted of an infusion flask connected by a rubber tube to the choledochostomy tube. A Murphy drip bulb was included in the system so that observations of flow could be made. The perfusion fluid was sterile physiologic salt solution. At the beginning of each experiment all gas bubbles were evacuated from the system, except for a small air gap in the Murphy drip bulb.

By elevating or lowering the infusion flask, the pressure within the duct system could be altered, and it could be read directly on a centimeter scale which was adjusted so that the zero point was at the estimated level of the common bile duct. In such a system, when the ducts were filled with the perfusion fluid, there was no flow as long as the sphincter resistance was equal to, or greater than, the pressure exerted by the column of solution. When the perfusion pressure exceeded the sphincter resistance there was a flow which could be detected through the Murphy drip bulb. Since the distensibility of the bile ducts is relatively slight, any flow of fluid resulting from small changes of pressure could be assumed to indicate that the fluid was flowing into the intestine and that the sphincter resistance had been overcome.

The column of saline solution was adjusted to the exact level at which it was just supported without allowing any flow. At that point a drop of fluid would hang from the nozzle of the Murphy drip bulb where it would oscillate with respiration but would not fall. The pressure then was read directly on the scale and was recorded as sphincter resistance at that moment.

Measurements of sphincter resistance were made successively at frequent intervals and were recorded. After thirty to ninety minutes of preliminary measurements, various types of stimulation were applied in order to observe their effects upon the sphincter mechanism. Except when it was desired to investigate the combined action of drugs, only one type of stimulation was applied during a single day.

CRITICISM OF THE METHOD

At the outset it must be emphasized that this method measures the total resistance to flow of fluid from the bile duct into the duodenum, including any influence of the duodenal musculature as well as the activity of the sphincter proper. The fact remains, however, that the method does measure the resistance offered by the functional sphincter mechanism.

Factors such as friction in the tubes produce slight errors, but Mann[153] has demonstrated that these are insignificant and the values obtained are reasonably accurate.

The outstanding objection to the procedure is that the subjects upon whom the experiments were performed all had undergone cholecystectomy, and therefore, were not entirely normal.

Since the time of Oddi, a number of investigators have recognized that extirpation of the gall bladder in certain animals, such as the dog, cat, and goat,[121, 176, 198] and also in man,[6, 120, 189-192] may be followed by dilatation of the biliary ducts. In other animals, such as the guinea pig,[204] this postoperative dilatation does not occur. Several explanations have been advanced to account for this change.

The most widely accepted explanation is that the dilatation is the result of increased intraductal pressure following cholecystectomy. This theory depends upon a persistence of action of the sphincter of Oddi. In the absence of the gall bladder, which normally acts as a pressure regulator, the increased pressure must be accommodated by dilatation of the duct.

Considerable evidence favors the validity of this explanation. Judd and Mann[121] and Colp, Doubilet, and Gerber[60] were able to prevent dilatation of the ducts by eliminating the action of the sphincter. The latter investigators also found that section of the sphincter in four animals with dilatation of the bile passages following cholecystectomy resulted in a return of the ducts to normal diameter. Potter and Mann[187] observed an increased pressure within the common bile duct following cholecystectomy in dogs. Furthermore, dilatation of the ducts does not occur, or is only slight, following extirpation of the gall bladder in animals with very low sphincter resistance such as the guinea pig and rabbit.*[204]

Puestow,[189, 192] on the other hand, stated that there is permanent loss of function of the sphincter of Oddi following cholecystectomy. He first observed this in dogs with a special type of biliary fistula in which the exteriorized duodenum was slit open. From his experience with human subjects with choledochostomy tubes, he believes that there is a similar loss of sphincter tone following cholecystectomy in man.

Our observations, and those of other investigators upon human subjects, however, contradict this view. Walters and his associates, Doubilet and Colp, and Layne and Bergh have demonstrated that a resistance to the flow of fluid from the bile duct into the duodenum still exists in patients who have had extirpation of the gall bladder, and, in fact, actual spasm of the sphincter can be produced.[13, 68, 132, 147, 226]

*Schmidt and Ivy[205] have studied many types of animals in regard to their output of hepatic bile, sphincter resistance, and physiologic capacity of the gall bladder, and have classified them into four groups: Group I with a large bile output, low sphincter resistance, and absent gall bladder (pocket gopher, pigeon, horse, and rat); Group II with a large bile output, low sphincter resistance, and gall bladder of low physiologic capacity (guinea pig, rabbit, and African bush rat); Group III with a small bile output, moderately high sphincter resistance, and gall bladder of low physiologic capacity (pig, sheep, goat, and cow); Group IV with a small bile output, high sphincter resistance, and gall bladder of high physiologic capacity (man, dog, cat, duck, chicken, mouse, striped gopher). The fact that dilatation of the ducts following cholecystectomy occurs in animals listed in Groups III and IV but not in those listed in Group II favors the theory that the dilatation depends upon a persistent action of the sphincter after removal of the pressure-regulating mechanism.

The more or less continuous flow of bile into the duodenum which has been observed in animals following cholecystectomy does not prove that the sphincter of Oddi has lost its tone. It indicates only that the sphincter resistance is smaller than the pressure under which the bile is being secreted. When the system has been filled with bile the pressure within the ducts must rise either until the sphincter resistance is exceeded, allowing flow into the duodenum, or until the secretory pressure is exceeded so that no more bile is formed. Variations in the sphincter resistance can make the flow of bile into the duodenum intermittent even in the absence of the gall bladder.

A second explanation of the dilatation of the ducts is based upon the assumption that there may be pressure transmitted into the common duct from the duodenum as a result of incompetence of the sphincter. This theory is based upon the observation that dilatation of the duct occurs following implantation of the common duct directly into the intestine[83] and also following cholecystoduodenostomy.[199] Under such conditions the action of the sphincter is eliminated. Bachrach and Fogelson,[3] however, suggest that in such cases the dilatation may be due rather to a temporary obstruction produced by swelling resulting from the operation.

Puestow[191] has offered a third theory, suggesting that the dilatation may be due to a loss of tonus of the wall of the bile ducts resulting from a local nervous derangement following cholecystectomy. Puestow, himself, recognized that the small amount of muscle in the wall of the ducts made such an explanation unlikely.

The evidence seems to indicate, therefore, that the ducts dilate because of persistence of activity of the sphincter mechanism. Whether the tone or response of the sphincter in man is altered by cholecystectomy cannot be stated definitely, since all studies have been made in individuals who have been operated upon. However, measurements of sphincter resistance in patients with choledochostomy tubes indicate that the sphincter does maintain tonus and activity following cholecystectomy, and the figures obtained are similar in range to those reported by many different investigators for the normal dog. In the absence of a method for studying the sphincter resistance in entirely normal human subjects, therefore, we are justified in accepting the results of experiments carried out according to the procedure which has been described.

NORMAL SPHINCTER RESISTANCE

Although the sphincter resistance cannot be determined in entirely normal individuals, we have considered the measurements obtained in individuals who had recovered from their operation, who were feeling well, and who had fasted for eight hours, as "normal." In such cases the sphincter usually withstood pressures between 9 and 23 cm. of

water. These figures are similar to those which Ivy and others quote as representing the normal intramural resistance in unanesthetized, fasting dogs. Our observations confirm the statement of Doubilet and Colp[68] that the average sphincter resistance in man is probably around 15 cm. of water.

Changes of a few millimeters in the intraductal pressure occurred during respiration, and marked changes were apparent during coughing, laughing, or vomiting, as a result of a temporarily increased intra-abdominal pressure. Even when the sphincter resistance appeared to be stabilized, changes of several centimeters' resistance occasionally occurred spontaneously without apparent cause. Often the initial measurements were slightly higher than those obtained subsequently.

IRRITABLE SPHINCTER

In some patients with choledocholithiasis, the sphincter remains irritable for several weeks, or even months, after the removal of a calculus from the common bile duct by operative procedure. In such cases the muscle readily goes into spasm and the intramural resistance may reach 30 or 40 cm. of water or more, and usually fluctuates through a wide range instead of becoming stabilized. We have supposed that such irritability is due to an inflammatory lesion (choledochitis secondary to stone). After several months of external drainage of the duct the irritability usually disappears and the sphincter apparently returns to "normal." McGowan and Henderson[148] also report that patients with an irritable sphincter have a lower "perfusion pain level" than patients with a more normal muscle.

These observations have led us to utilize sphincter resistance tests as one of the criteria for determining the proper time for removal of a choledochostomy tube.*

As early as 1761, Morgagni[164] suspected that spasm of the bile duct might produce clinical disorders. Oddi, with his more complete understanding of the anatomical arrangement of the muscular sphincter of the duct, advanced this proposition. More recently the importance of sphincter spasm in its relation to symptoms has been emphasized by Schmieden and Niessen,[206] John Berg,[8] Meltzer,[160] Westphal, Gleichmann, and Mann,[239, 240] Ivy and Sandblom,[113] Walters,[226] Best and Hicken,[21] and others.

*The criteria which we use to assist us in determining the proper time to remove a choledochostomy tube are: (1) cholangiographic evidence that the biliary tree is structurally normal, that no filling defects suggestive of stone are present, and that the contrast medium empties readily into the duodenum; (2) direct evidence that the sphincter resistance is normal and that the sphincter is not irritable; (3) subjective comfort of the patient, and lack of drainage around the tube when the catheter is clamped. If necessary, bile duct drainage may be continued for long periods of time without ill effect. One of Wangensteen's patients has carried such a tube for eight years, coming to the clinic periodically for change of the catheter. In the case of prolonged drainage it is necessary to change the choledochostomy tube at frequent intervals. Unless the external drainage of bile is complete or almost complete, it is not necessary to return the bile by mouth.

Presumably a purely functional derangement (biliary dyskinesia or biliary dyssynergia) may produce such spasm, but probably more often the irritability of the sphincter is on an organic basis. Snell, McGowan, and Butsch[215] have suggested that local inflammatory processes may induce sphincter spasm, and Ivy and Goldman[110] have pointed out that inflammation of the ampulla could make the muscle hyperirritable. Reflex contractions of the sphincter secondary to disturbances in more remote organs have not been demonstrated in man.

THE RESPONSE OF THE SPHINCTER TO FOOD

Many investigators have observed that the ingestion of food is followed by a flow of bile into the intestine. However, one may not infer from such an observation that food causes the sphincter to relax, since it is well known that certain food substances may cause both an increased secretion of bile and contraction of the gall bladder.

Winkelstein and Aschner,[244] Cole,[58] McMaster and Elman,[75, 150] and others have reported that food influences the sphincter to relax in dogs. In human subjects there is little information concerning the question. Carter[56] has stated that the external drainage of bile from a choledochostomy tube is decreased after a meal, indicating relaxation of the sphincter. Walters[227] described one patient in whom biliary colic, produced by morphine, was relieved partially after eating. Best and Hicken[24] inferred from cholangiographic evidence that cream and olive oil produced relaxation of the muscle. Using direct measurements of sphincter resistance, Doubilet and Colp[68] found that, in one case, a full meal did not influence the sphincter; in another patient a meal of soup, two eggs, and ice cream had no effect; and, in a third case, clear chicken soup produced slight relaxation.

Since information concerning the response of the human sphincter to food is fragmentary, I have[12] carried out a series of 34 experiments in an attempt to discover the effects of a fatty meal, a protein meal, and a carbohydrate meal.

Before undertaking these studies, it was established that the ingestion of water alone did not influence the sphincter tone. The effects of the different types of meals then were tested.

A fatty meal consisting of two raw egg yolks mixed in a glass of cream and flavored with sugar was given to 15 patients. In 4 additional cases a meal of 30 to 60 c.c. of olive oil was given. The oil was given by mouth in 2 cases and by duodenal tube in the others.

The protein meal, which was given to 4 patients, consisted of the whites of two eggs and two slices of lean, trimmed beef.

The carbohydrate meal, which was given to 8 patients, consisted of 200 c.c. of sweetened fruit juice and two thin slices of unbuttered white bread with fruit jam. In 3 other cases the effect of intravenous ad-

ministration of 250 to 500 c.c. of 10 per cent glucose solution was studied.

The egg yolk meal produced sphincter relaxation in 14 of the 15 experiments. The relaxation began following an average delay of four minutes after ingestion of the meal. Previous to the relaxation in one-half of the cases there was a brief initial increase in sphincter resistance. This initial elevation of sphincter tone might account for the frequently occurring "two-minute pause" preceding the initial phase of gall bladder emptying as described by Boyden.[35] The average maximum fall of sphincter resistance was 7 cm. of water pressure and occurred twenty-one minutes after ingestion of the food (average). The total average duration of the first phase of relaxation was thirty-four minutes. Subsequent fluctuations of sphincter resistance included relaxations and contractions of the muscle capable of determining later phases of gall bladder emptying. Periods of relaxation sometimes were observed for as long as two or three hours after the meal.

In the experiments in which olive oil was administered the effect was insignificant. The negative result might be due to the fact that fresh olive oil was used. Rost[198] has reported that old olive oil produces a flow of bile in dogs, but that fresh oil is ineffective. Best and Hicken[22] state that warm olive oil produces relaxation of a spastic sphincter, and that it is effective on the choledochal side as well as when it is placed into the duodenum.

The protein meal produced sphincter relaxation only once in 4 experiments. In the other 3 cases there was no effect. In dogs, Jacobson and Gydeson[116] observed some relaxation from protein stimulation, but McWhorter[151] found no effect.

Neither a carbohydrate meal nor 10 per cent glucose solution administered intravenously had any significant effect upon the sphincter.

These observations may be correlated with the well-known facts concerning the effects of food upon the gall bladder. Fats produce the greatest contraction of that organ, proteins rank next, and carbohydrates are practically ineffective in causing gall bladder evacuation.

Since the subjects upon whom the experiments were performed had undergone cholecystectomy, it is apparent that the responses of the sphincter of Oddi to food are not dependent upon the presence of the gall bladder. Contraction of the gall bladder and relaxation of the sphincter following a fatty meal appear to be independent reactions to the same stimulus.

THE EFFECT OF SODIUM DEHYDROCHOLATE

It is well known that bile and bile salts stimulate an increased secretion of bile both in experimental animals and in man.[170, 202, 248] The use of these substances as therapeutic agents makes it desirable to learn their effect upon the constituent parts of the biliary system. It has been reported that they produce relaxation of the gall bladder[5, 106] in addition

to their choleretic action. According to Winkelstein and Aschner,[244] bile salts produce a decrease of sphincter tone in dogs.

In 8 human subjects we studied the effect of the intravenous injection of 5 to 10 c.c. of 20 per cent sodium dehydrocholate. The results were variable. Slight relaxation of the sphincter occurred in 4 cases, there was no effect in 3 cases, and in 1 case an increased tone of the sphincter was produced. Best and Hicken[20, 24] reported an increased intraductal pressure after administration of sodium dehydrocholate to human subjects with choledochostomy tubes.

THE RESPONSE OF THE SPHINCTER TO DRUGS

In a series of 176 experiments, the effects upon the sphincter resistance following the administration of various drugs were studied. In the case of some of the drugs no comparable observations have been reported previously. In other cases the observations of earlier investigators were confirmed or contradicted. The obvious clinical value of knowing the action of various drugs upon the sphincter of Oddi requires no comment. Beyond that, however, certain inferences concerning the physiology of the sphincter may be drawn from the data which have been secured.

Morphine.—In 8 experiments we observed that morphine sulfate, in doses of $\frac{1}{12}$ to $\frac{1}{6}$ gr. subcutaneously, produced a prompt and prolonged increase in sphincter tone. (The increase in sphincter tone following the administration of any of the opiates which are included in this review may persist for more than two hours.)

Reach,[193-195] working with guinea pigs and rabbits, was the first to demonstrate that morphine produced a contraction of the sphincter of Oddi (1913). This was confirmed in dogs by Iwanaga,[115] Kitakoji,[126] and Lueth.[138] Butsch, McGowan, and Walters[55] showed that the same effect occurred in man, and our experiments, as well as those of Doubilet and Colp,[68] confirm this observation. Butsch, McGowan, and Walters reported that the effect of morphine was evident within two and one-half to five minutes after injection of the drug, and reached its maximum within fifteen minutes. Confirmatory results have been obtained by others.

J. Berg,[8] Butsch, McGowan, and Walters,[55] and Nygaard[175] have reported patients in whom morphine precipitated attacks of biliary colic. We have observed similar cases. Sometimes the sphincter spasm and the pain in such instances may be relieved by the administration of amyl nitrite[55, 175] or by a fatty meal.[11]

Codeine (Methyl Morphine).—Butsch, McGowan, and Walters[55] have reported that codeine produces a prolonged contraction of the sphincter, but that the elevation of sphincter tone is not as great nor as swiftly produced as in the case of morphine. In 6 experiments, using a 1 gr.

dose of codeine administered subcutaneously, our results confirmed the observations of Butsch, McGowan, and Walters.

Pantopon (Pantopium Hydrochloride).—Pantopon consists of the isolated alkaloids of opium in their natural proportions. In 5 experiments we observed an effect from pantopon almost exactly like the effect produced by morphine. A prompt contraction of the sphincter followed the injection of ⅓ gr. doses of the drug, and the increased intramural resistance persisted for long periods of time.

Reach[195] was the first to show the action of this drug upon the sphincter (1920). He observed that it caused increased sphincter resistance in the guinea pig. Butsch, McGowan, and Walters[55] demonstrated a similar effect in man. Nygaard[175] reported having observed a patient with postcholecystectomy pain in whom pantopon induced attacks of biliary colic.

Dilaudid (Dihydromorphinone Hydrochloride).—Dilaudid is said to exert less effect upon the alimentary canal than morphine, but we found the effect of the two drugs upon the sphincter to be almost identical. In 4 experiments the subcutaneous injection of dilaudid (in doses of $\frac{1}{32}$ gr.) was followed by a prompt contraction of the sphincter, with a prolonged elevation of the intramural resistance. Butsch, McGowan, and Walters[55] have reported similar findings.

Amyl Nitrite.—The nitrites and the organic nitrates which are reduced to nitrites in the body decrease the tone of smooth muscle generally, and as a result of that property have proved beneficial in certain cases of biliary colic.

In 1915, Lieb and McWhorter[136] demonstrated that amyl nitrite produced a loss of tonus in the isolated gall bladder of the dog. Reach,[195] however, was unable to show any significant effect upon the sphincter in guinea pigs.

Butsch, McGowan, and Walters[55, 147, 233] in their studies on human subjects found that inhalation of amyl nitrite immediately lowered an elevated intrabiliary pressure, whether the elevated pressure was spontaneous or the result of a previous injection of morphine. If pain was associated with the elevated pressure, it was relieved by the drug. Relief from biliary colic after inhalation of amyl nitrite has been reported subsequently by others.[175, 225]

Our experiments (11 cases) confirmed the observation that amyl nitrite produced relaxation of the sphincter. In most cases the relaxation was almost immediate, and the sphincter resistance returned to the original level within ten minutes. Occasionally, however, in the presence of a spastic sphincter, relaxation did not occur. In such instances the pain associated with the sphincter spasm did not disappear. Clinical experience supplements this observation, for many cases of biliary colic cannot be relieved by amyl nitrite.

Nitroglycerin (Glyceryl Trinitrate).—In 1936 Best and Hicken[22-26] and Butsch, McGowan, and Walters[55, 146] independently described the relaxing effect of nitroglycerin upon the sphincter, showing that it produced a more prolonged, but less marked effect than amyl nitrite. Our observations were confirmatory. Nitroglycerin (1/100 gr. tablet under the tongue) produced relaxation of the sphincter which was maintained for fifteen to sixty minutes in 6 of our 7 cases. In the other case a spasm of the sphincter occurred. Relief from biliary colic after the administration of nitroglycerin has been described by a number of clinicians.[18-26, 55, 146, 147, 175, 215, 226-234]

Erythrol Tetranitrate.—The action of erythrol tetranitrate upon smooth muscle develops slowly but persists for long periods. It is desirable to know, therefore, whether this drug produces a prolonged relaxation of the sphincter of Oddi. Two experiments were carried out (using 1 gr. of erythrol tetranitrate by mouth), and in neither case did the drug produce any significant change in sphincter resistance.

Theophyllin Ethylenediamine.—Snell, McGowan, and Butsch[215] reported one patient in whom the intravenous injection of theophyllin ethylenediamine produced relaxation of the sphincter, and Butsch, McGowan, and Walters[55] demonstrated that this drug could decrease the intrabiliary pressure which had been increased by the administration of codeine. In 5 experiments (using 0.24 Gm. of the drug) we were unable to demonstrate any significant effect upon the sphincter resistance after the intravenous injection of theophyllin ethylenediamine, even though the original intramural resistances were as high as 20 cm. of water in 2 of our cases. We did not measure the effect of the drug in any case with a spastic sphincter.

Trasentin (Diphenylacetyldiethylaminoethanol).—Spier, Neuwelt, and Necheles[216] demonstrated that trasentin caused relaxation of the gall bladder of the dog, and assumed that it produced a similar relaxation of the sphincter of Oddi. Macdonald[142] stated that the drug would decrease sphincter tonus in human subjects. We measured the sphincter resistance in 5 patients after the intramuscular injection of 75 mg. doses of trasentin. In 2 of the cases there was no change in the intramural resistance, and in the remaining 3 instances the relaxation was slight.

Papaverine.—Papaverine is said to relax the tonus of smooth muscle without paralyzing contractility. However, in 3 experiments we found that it did not influence the sphincter resistance when given in 1/2 gr. doses. Neither did it prevent the elevation of the intramural resistance following the administration of morphine. Similar findings have been reported by Butsch, McGowan, and Walters[55] and Doubilet and Colp.[68]

On the other hand, Reach[195] reported that it produced sphincter relaxation in the guinea pig, and Blass[28] stated that when papaverine was introduced into the duodenum of human subjects it caused a flow of

bile in most cases. The flow of bile into the duodenum, however, cannot be accepted as an indication of sphincter relaxation.

Magnesium Sulfate.—The use of magnesium sulfate for "nonsurgical biliary drainage" makes the study of its action upon the sphincter of Oddi of especial interest.

In 1917, Meltzer[160] suggested that if magnesium sulfate were introduced into the duodenum it might cause relaxation of the sphincter, and probably also contraction of the gall bladder ("Law of Contrary Innervation"). Lyon[140, 141] applied this suggestion to human patients and observed that the introduction of this drug into the duodenum induced a flow of bile which was light yellow at first (A bile), but which later became darker and more viscid (B bile).

McWhorter,[151] Jacobson and Gydeson,[116] Winkelstein and Aschner,[244] Iwanaga,[115] Shi,[213] and others reported that it caused relaxation of the sphincter in dogs. Lueth[138] stated that 5 c.c. of 25 per cent solution produced a temporary decrease in sphincter resistance with a return to the original level after one or one and one-half minutes. Instillation of 20 c.c. of the same solution resulted in either an increase or no change in intramural resistance. Puestow[189] stated that magnesium sulfate had an inconstant stimulating effect upon the duodenal musculature in dogs, but no evident independent activity upon the orifice of the choledochus. Gantt and Volborth[81] observed that the introduction of magnesium sulfate solution into the duodenum of the dog was not followed by the expulsion of bile and that the drug did not have any constant effect upon the pressure within the gall bladder and bile ducts. Boyden and Birch[43, 44] noted that magnesium sulfate given by mouth or by duodenal tube to cats did not induce emptying of the gall bladder.

In one human subject, Ivy, Voegtlin, and Greengard[114] apparently relieved spasm of the sphincter (which had been provoked by the intravenous injection of a secretin-cholecystokinin mixture) by the instillation of magnesium sulfate into the duodenum. Doubilet and Colp[68] and Best and Hicken[25] also reported sphincter relaxation following the administration of magnesium sulfate in man.

Bergh and Layne[15] observed that a 12.5 Gm. dose of magnesium sulfate may produce any one of four types of effects upon the sphincter of the common bile duct in man. It may produce relaxation with or without an initial contraction, it may produce an initial contraction followed by a return to the original tonus level, or there may be no effect. Sphincter relaxation occurred thirty-three times in a series of forty-two observations. The relaxation, however, frequently was preceded by a temporary increased intramural resistance.

There has been some question as to the effectiveness of the oral route of administration of magnesium sulfate as compared to duodenal instillation. Meltzer[160] stated that the salt is ineffective when given by mouth. Eppinger[77] also advised duodenal instillation of the drug.

Dunn and Connell[72] disagreed, and stated that one would not expect any inactivating change in the magnesium sulfate to occur during its passage through the stomach. Best and Hicken[25] noted that the drug produced a relaxation of the sphincter (as inferred from cholangiograms) when administered orally or intraduodenally. Bergh and Layne[15] found that the relaxing effect of magnesium sulfate is similar whether the drug be given by mouth or administered intraduodenally. However, this relaxing effect is not great. It is less constant and weaker than the effect produced by amyl nitrite or by a fatty meal. Furthermore, the same authors in conjunction with Boyden[133] recently have found that magnesium sulfate acts primarily on the gall bladder and not on the sphincter in causing a flow of bile into the duodenum.

Calcium Chloride and Calcium Gluconate.—Eleven experiments were carried out to study the effect of the intravenous injection of 10 c.c. of 10 per cent solutions of calcium chloride and calcium gluconate. The results were not constant. Contraction of the sphincter followed the injection of the drug in 3 cases, and slight relaxation occurred twice. In the remaining 6 patients there was no significant effect.

Butsch, McGowan, and Walters[55] reported that the intravenous injection of calcium chloride failed to lower the pressure within the bile duct in human patients. Winkelstein and Aschner[244] stated that the intraduodenal injection of this drug produced an increased tonus of the sphincter of Oddi in dogs.

Hochman[104] and Lampson and Simeone[131] reported having observed patients in whom relief from biliary colic followed the intravenous injection of calcium salts. In the light of our experiments it seems unlikely that such relief could be due to relaxation of sphincter spasm. Neither is it likely that the relief is due to relaxation of the gall bladder, since it has been reported that calcium salts produce augmentation of tonus rhythm[224] and some evacuation[32] of that organ.

Ethyl Alcohol.—The effect upon sphincter resistance of the intraduodenal instillation of 15 to 25 c.c. of 95 per cent ethyl alcohol diluted to 50 c.c. with water was studied in 3 experiments. In 1 case there was no effect, and in each of the other 2 there was a very slight relaxation.

Nygaard[175] observed a patient with postcholecystectomy colic in whom the ingestion of alcohol initiated the pain. Butsch, McGowan, and Walters[55] stated that, in man, 30 c.c. of alcohol had no effect upon the pressure within the bile duct. Cole[58] reported that, in the dog, alcohol in the stomach usually produced no effect upon the sphincter resistance, but occasionally it caused a definite relaxation.

Hydrochloric Acid.—Reports concerning the effect of hydrochloric acid upon the sphincter of Oddi have been contradictory. A number of investigators reported that the application of dilute hydrochloric acid to the duodenal mucosa produced a discharge of bile,[1, 115, 181, 198]

while others reported the opposite effect.[44, 51] Oddi[178] found that acid caused a contraction of the sphincter in animals. Archibald[2] reported similar findings. Jacobson and Gydeson[116] stated that the introduction of 0.4 per cent acid was followed by an initial sphincter contraction and increased intraductal pressure, but with a subsequent decrease. On the other hand, Cole,[58] Iwanaga,[115] and Giordano and Mann[83] observed that hydrochloric acid decreased the resistance of the sphincter.

In human subjects Doubilet and Colp[68] found that the instillation into the duodenum of 0.9 per cent hydrochloric acid caused a spasm of the sphincter. We have confirmed that observation in 1 case with 0.5 per cent acid.

Histamine.—Histamine, when injected subcutaneously, generally produces stimulation of the tone of smooth muscle, but the susceptibility of different muscles varies, and some are not affected at all. The intestinal muscle is only slightly affected, but the drug does produce some contraction of the gall bladder.[94, 101, 169]

The effect upon the sphincter of Oddi was studied in 6 experiments after the subcutaneous injection of 0.5 mg. histamine phosphate. In 3 patients there was no effect. In the other 3 there was relaxation, preceded in 1 case by an initial contraction.

Reach[195] reported that histamine exerted no significant effect upon the sphincter in guinea pigs. Lueth[138] found that it caused an increased intramural resistance in dogs. Butsch, McGowan, and Walters[55, 147] observed that, in man, the injection of 0.6 mg. histamine had no effect upon the pressure within the common bile duct.

Epinephrine.—Epinephrine has been reported to cause contraction, relaxation, or to have no effect upon the gall bladder.[5, 32, 50, 57, 63, 94, 224] It appears that its effect must be variable. There is a similar disparity in reports concerning its action upon the sphincter. McWhorter[151] reported that epinephrine increased the tension of the sphincter in dogs. Lueth[138] stated that it decreased the intramural resistance in doses of 1 to 5 c.c. of 1:10,000 solution, but that the opposite effect usually was obtained with smaller doses. Winkelstein and Aschner,[244] Iwanaga,[115] and Shi[212] reported relaxation of the sphincter in dogs following the administration of epinephrine. Kitakoji[126] stated that there was no significant effect from the drug. Butsch, McGowan, and Walters,[55] Best and Hicken,[25] and Doubilet and Colp[68] reported that, in man, there was little or no effect upon the sphincter following injections of epinephrine.

We studied the effect of epinephrine (10 minims of 1:1,000 solution subcutaneously) upon the sphincter of Oddi in 9 experiments. The results were variable. There was no significant effect in 2 cases; in 4 cases relaxation of the sphincter was produced; and in 3 cases injection of the drug was followed by an increased intramural resistance.

Ephedrine.—In 4 experiments the results of the subcutaneous injection of 50 mg. of ephedrine sulfate, like those following epinephrine, were variable. In 1 case the drug produced contraction of the sphincter, in another patient it caused a temporary relaxation, and there was no effect in the remaining 2 cases.

Butsch, McGowan, and Walters[55] and Best and Hicken[25] reported that ephedrine had no effect upon the human sphincter.

Benzedrine Sulfate (Benzyl Methyl Carbinamine Sulfate).—Benzedrine has been reported to cause relaxation of the gall bladder in animals,[78, 169] and to have no effect upon the gall bladder in man.[208] There have been no reports concerning its action on the sphincter of Oddi.

The effect of the subcutaneous injection of 20 to 30 mg. of benzedrine sulfate was studied in 6 experiments. The results were somewhat variable, but indicated that the effect was probably insignificant.

Caffeine Sodium Benzoate.—In 8 experiments the subcutaneous injection of 7.5 Gm. of caffeine sodium benzoate was found to produce no significant effect upon the sphincter resistance.

Reach[195] stated that caffeine citrate produced contraction of the sphincter of Oddi in guinea pigs. Lueth,[138] on the other hand, reported that caffeine caused no change in the intramural resistance in dogs, while Iwanaga[115] stated that it produced relaxation in dogs and rabbits. Butsch, McGowan, and Walters[55] reported that caffeine sodium benzoate produced no effect upon the sphincter in human subjects.

Atropine.—In 11 experiments we studied the effect of the subcutaneous administration of atropine sulfate in doses of $\frac{1}{50}$ to $\frac{1}{100}$ gr. In 10 cases there was no significant change in the intramural resistance, and in 1 case the resistance was slightly decreased.

Clinicians have assumed that atropine paralyzes the innervation of the smooth muscle of the sphincter of Oddi, causing relaxation, but there is little evidence that this actually occurs in man. Volini and O'Brien[225] have pointed out that atropine almost always fails to relieve biliary colic.

Butsch, McGowan, and Walters[55] found no effect from atropine upon the sphincter in man. Doubilet and Colp[68] stated that the drug does not inhibit sphincter spasm following the injection of morphine, but that it does prevent spasm following the intraduodenal instillation of hydrochloric acid. They also reported one case with an irritable sphincter in which atropine seemed to decrease the irritability. Pribram[188] reported a patient in whom cholangiography showed a spastic sphincter with no emptying for almost an hour. After the intravenous administration of 1 mg. of atropine, a roentgenogram showed the contrast medium to be flowing into the duodenum.

The preponderance of evidence, including our own, indicates that atropine does not cause the human sphincter to relax. Most experimenters agree that in animals, on the contrary, atropine does produce

relaxation of the sphincter of Oddi. Iwanaga,[115] Winkelstein and Aschner,[244] Kitakoji,[126] Lueth,[138] and Shi[212] reported relaxation of the sphincter in dogs after the administration of atropine. On the other hand, Reach[195] observed that the drug usually produced contraction of the sphincter in guinea pigs, and Cole[58] stated that it had no effect upon the sphincter resistance in dogs.

On the basis of animal experiments showing relaxation of the sphincter following the administration of atropine and contraction following the injection of pilocarpine, several investigators have inferred that the autonomic nervous system plays an important role in the regulation of sphincter activity in the dog. In man, however, we have observed that atropine and pilocarpine do not influence the intramural resistance. This suggests that the parasympathetic nervous system does not play an important part in the regulation of sphincter activity in human subjects.

Acetyl-Beta-Methylcholine Chloride (Mecholyl).—In 2 patients we studied the effect upon the sphincter of the subcutaneous injection of 15 and 20 mg. doses of acetyl-beta-methylcholine chloride. In 1 case a contraction of the sphincter followed the injection of the drug and persisted for more than thirty minutes. In the other, there was little change except for a short period of increased sphincter resistance.

Kitakoji[126] reported that acetylcholine caused contraction of the sphincter of Oddi in dogs. Lueth's[138] findings were similar, but were not constant. In two of his experiments the intramural resistance decreased, even though the intraduodenal pressure remained unchanged or increased. Butsch, McGowan, and Walters[55] observed no effect upon the intrabiliary pressure in man following administration of the drug.

Pilocarpine.—In 8 experiments we measured the effect of the subcutaneous injection of 6 mg. of pilocarpine upon the sphincter resistance in human subjects. In 7 patients there was no change in intramural resistance, and relaxation was produced in 1 case. The importance of this observation in relation to inferences concerning the mechanism of regulation of the sphincter activity already has been discussed.

In animals, on the other hand, pilocarpine causes contraction of both the gall bladder and the sphincter. Reach[195] was the first to study the effect of this drug upon the sphincter (1920). He observed that it caused a prompt contraction in guinea pigs. Winkelstein and Aschner,[244] Iwanaga,[115] Kitakoji,[126] Lueth,[138] and Shi[213] observed a similar effect upon the sphincter resistance in dogs.

Westphal noted that, in pregnant women studied by duodenal aspiration, the initial effect of pilocarpine was to inhibit the flow of bile. Subsequently there was a flow of dark bile. Westphal attributed that response to a temporary spasm of the sphincter of Oddi resulting from pilocarpine stimulation. Since that time, however, Tanturi and Ivy[220]

have demonstrated that pilocarpine causes first an inhibition and then a stimulation of the secretion of bile, so Westphal's observations could be explained without considering any activity of the sphincter.

Prostigmine (Dimethyl Carbamic Ester of Oxyphenyl-Trimethyl-Ammonium Methyl Sulfate).—Tanturi and Ivy[220] reported that prostigmine caused a primary inhibition of bile secretion, lasting five to ten minutes, followed by stimulation. There has been no information concerning its effect upon the sphincter.

In 6 experiments we observed that the subcutaneous injection of 1 c.c. of 1:4,000 solution of prostigmine did not influence the sphincter of Oddi in 4 of the human subjects. Sphincter relaxation followed injection of the drug in 1 patient, and in 1 case there was slight sphincter contraction.

Posterior Pituitary Extract.—Lueth[138] and Shi[213] reported that posterior pituitary extract caused relaxation of the sphincter of Oddi in dogs, while Cole[58] stated that it produced an increase in the sphincter resistance.

In 4 human subjects we observed no significant effect upon the sphincter after the subcutaneous injection of posterior pituitary extract (1 c.c. pituitrin).

SUMMARY

Anatomists have demonstrated a distinct sphincter of the common bile duct, and physiologic studies have indicated that it can function independently of the intestinal musculature. In addition to the action of the intrinsic sphincter, it is possible that duodenal motility and tone may influence the resistance to bile flow. However, in man the anatomical arrangement of the window in the duodenal muscle through which the bile duct enters the intestine is such that duodenal peristalsis probably exerts a minimal effect.

Functions which have been attributed to the sphincter of Oddi are: (1) making possible the filling of the gall bladder, (2) preventing the regurgitation of intestinal contents into the bile duct, (3) regulating the discharge of bile into the duodenum, and (4) erecting the papilla.

The discharge of bile into the duodenum is dependent upon the tonus of the sphincter, the activity of the gall bladder, and the pressure of bile secretion. In order to secure information concerning the effect of various types of stimulation upon the sphincter mechanism, the resistance to the flow of fluid may be studied in patients with intubation of the common bile duct.

Since there is no method allowing measurement of the sphincter resistance in entirely normal human subjects, we have considered the figures obtained in individuals who had recovered from their operations, who were feeling well, and who had fasted for periods of six or eight hours, as "normal." In such cases the sphincter withstands

pressures between 9 and 23 cm. of water, and usually the sphincter resistance is around 12 to 15 cm. of water.

Changes of a few millimeters in the intraductal pressure occur during respiration, and marked changes occur during coughing, laughing, or vomiting as a result of a temporary increase in intra-abdominal pressure. Even when the sphincter resistance appears to be stabilized, changes of several centimeters' resistance may occur spontaneously from time to time.

In some patients the sphincter remains irritable for weeks after removal of a calculus from the common bile duct. In such instances the muscle readily goes into spasm. After prolonged external drainage of the bile duct, the irritability usually disappears and the sphincter returns to "normal."

The ingestion of a fatty meal consisting of egg yolks and cream causes relaxation of the sphincter; proteins occasionally produce relaxation, but neither a carbohydrate meal nor glucose given intravenously has any significant effect. Water taken by mouth also fails to produce a change in sphincter resistance.

Morphine, codeine, pantopon, and dilaudid cause contraction of the sphincter of Oddi.

Amyl nitrite and nitroglycerin produce relaxation of the sphincter, but atropine does not. Erythrol tetranitrate is ineffective. Trasentin, epinephrine, ephedrine, histamine, and ethyl alcohol sometimes produce sphincter relaxation, but the effects are variable.

Magnesium sulfate may produce sphincter relaxation with or without an initial contraction; it may produce an initial contraction followed by a return to the original tonus level, or there may be no effect. Relaxation, when it does occur, usually is not great, and contraction of the gall bladder following administration of magnesium sulfate probably is more important than sphincter relaxation in producing a flow of bile into the duodenum in patients with a functioning gall bladder.

Atropine, pilocarpine, papaverine, posterior pituitary extract, benzedrine, prostigmine, caffeine sodium benzoate, and theophyllin ethylenediamine have no significant effect upon the sphincter. The effects of sodium dehydrocholate, histamine, epinephrine, ephedrine, calcium gluconate and calcium chloride are not constant.

Severance of the nerves in the hepatoduodenal ligament is not recommended as a means of lowering sphincter resistance.

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Book Reviews

Macleod's Physiology in Modern Medicine. Edited by Philip Bard. Ed. 9. Pp. 1256, with 387 illustrations. St. Louis, 1941, The C. V. Mosby Co. $10.

The first edition of *Macleod's Physiology* appeared in 1918 and was immediately recognized as an important contribution in this field of endeavor. The fact that it is now going into its ninth edition is sufficient evidence of its establishment as a distinguished and authoritative text.

The arrangement of the present edition is similar to that of the eighth edition which "was largely rewritten by a group of authors each of whom contributed a section devoted to one of the major fields of physiology." Besides the authors who contributed to the previous edition there have been added in the present edition, Howard J. Curtis who has rewritten the chapters on electrical excitation and conduction of the nerve impulses and Walter S. Root who has contributed a chapter on the urinary bladder. The extensive scope of the book is indicated by the bibliography which covers sixty-six pages. These references are placed at the end of the volume and are conveniently arranged according to the major section and portion of the text covered. This textbook, which has been brought up to date, not only fulfills its original purpose of serving "as a guide to the clinical application of physiology and biochemistry," but continues to be an invaluable, ready, and reliable reference to clinicians interested in experimental investigations.

The Intervertebral Disc: With Special Reference to Rupture of the Annulus Fibrosus With Herniation of the Nucleus Pulposus. By F. Keith Bradford and R. Glen Spurling. Ed. 1. Pp. 158, with 45 illustrations. Springfield, Ill., Charles C Thomas, Publisher. $4.

The Intervertebral Disc, a valuable 150-page monograph, is dedicated to Dr. W. Jason Mixter, Dr. Joseph S. Barr, and Dr. Aubrey O. Hampton, the neurosurgeon, orthopedist, and radiologist whose contributions to the knowledge of intervertebral disc lesions have done so much in placing the surgical treatment of this common and incapacitating condition on a practical basis. The book gives an excellent description of the development and anatomy of these structures, as well as of the physiologic and pathologic conditions which may lead to rupture of the annulus fibrosus and herniation of the nucleus pulposus.

The authors' concept of the innervation of the discs and the posterior longitudinal ligament is of special interest, because it accounts for the diffuse lumbar backache which is often present in addition to the sharp sciatic pain. So also is their evidence that a differential diagnosis can be made between a protrusion of the disc at the fourth and one at the fifth lumbar interspace by careful neurologic examination. In typical cases this is of great value and sometimes obviates the need for contrast myelography. Besides containing a clearly drawn picture of the clinical and radiologic findings in the common syndrome of herniation of the two lowest lumbar discs, the rarer instances of protrusion in the cervical and other regions are not neglected. It is unfortunate that the manuscript should have been sent to the printers too early for the authors to have had experience with Kubik and Hampton's

technique for removing intraspinally injected lipiodol, because this maneuver has so effectively overcome the current objections to the use of accurate contrast localization of these lesions. The surgical description of removing the protruded disc through a limited hemilaminectomy incision is given in a most lucid fashion and the results analyzed in a series of 166 cases. Whether to include a spinal fusion or not remains the most debated point in the treatment of these lesions. The authors, who belong to the nonfusion school, have perhaps dismissed this question with too little consideration.

In addition to presenting the authors' experience in a large series of intervertebral disc lesions, the volume contains a valuable review of the formidable literature which has accumulated on this much discussed topic. The book should appeal particularly to neurosurgeons and orthopedists, and should be of special help to newcomers in these fields.